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REVIEW

Delay in the diagnosis of paediatric brain tumours: a systematic review

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Abstract

Purpose A delay in obtaining a diagnosis has been associated with inferior outcomes across several cancer types, including paediatric brain tumours. However, no clear evidence exists in this population. We aimed to quantify the reported pre-diagnostic symptom interval (PSI) as the time from onset of first symptoms to diagnosis in the literature, in addition to evaluating the relationship between delay and outcomes, including survival.

Methods A systematic review of the literature was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. MEDLINE, Wiley Online Library, Web of Science and EMBASE databases were searched. We considered all sources published between 1st January 2010 and 5th November 2022. Children and adolescents aged under 21 years, with new symptomatic primary brain tumour diagnoses, were included.

Results Of 3123 studies identified, 11 were included for analysis. Owing to study heterogeneity, a quantitative meta-analysis was not feasible; however, a narrative synthesis was performed. The median reported PSI varied widely, ranging between 28 and 760.8 days. We failed to identify a significant association between prolonged PSI and inferior overall survival. Few factors were consistently associated with prolonged PSI, amongst them only tumour grade and patient age.

Conclusion Delayed diagnosis of paediatric brain tumours was not associated with inferior survival within this review. This 'waiting time' paradox appears to result from several confounding factors including tumour biology, patient population and key systematic factors that were inconsistently reported. Diagnostic interval clearly presents a complex variable, reflected further by disparity in the reporting of delay within the literature. Ultimately diagnostic interval is unlikely to provide a meaningful representation for all tumour types and should not detract from sharp clinical acumen and prompt diagnosis.

Keywords Diagnostic delay · Childhood brain tumours · Central nervous system tumours · Pre-diagnostic symptom interval

Introduction

Brain tumours are the most common solid tumours of childhood [1–3]. Minimising the interval from onset of symptoms to diagnosis has the potential to improve survival and has been the focus of large public health and professional campaign drives [4–6]. The Royal College of Paediatrics and Child Health (RCPCH) in conjunction with the National Institute of Clinical Excellence (NICE) published 'The Brain Pathway Guideline' in response to research indicating time from symptom onset to diagnosis in childhood brain tumours was greater in the United Kingdom (UK) than in other countries [1]. Recognition of frequently non-specific features of intracranial lesions can be challenging in primary care and may be exaggerated in children. Such ambiguity in presentation is believed to contribute to diagnostic delay. 'HeadSmart' formed the resulting campaign by the RCPCH to raise awareness of presenting features [7]. A review of the campaign in 2013 estimated the total diagnostic interval (TDI) for childhood brain tumours to be 6.7 weeks, down from 14.4 weeks in 2006 [8]. Poor outcomes are often attributed to delays in the cancer diagnosis; however, this relationship is not well described in the context of paediatric brain tumours.

Defining a 'delay' can be challenging. A frequent challenge is the variable language used to describe intervals of the diagnostic pathway [9]. 'The Anderson Model' is a

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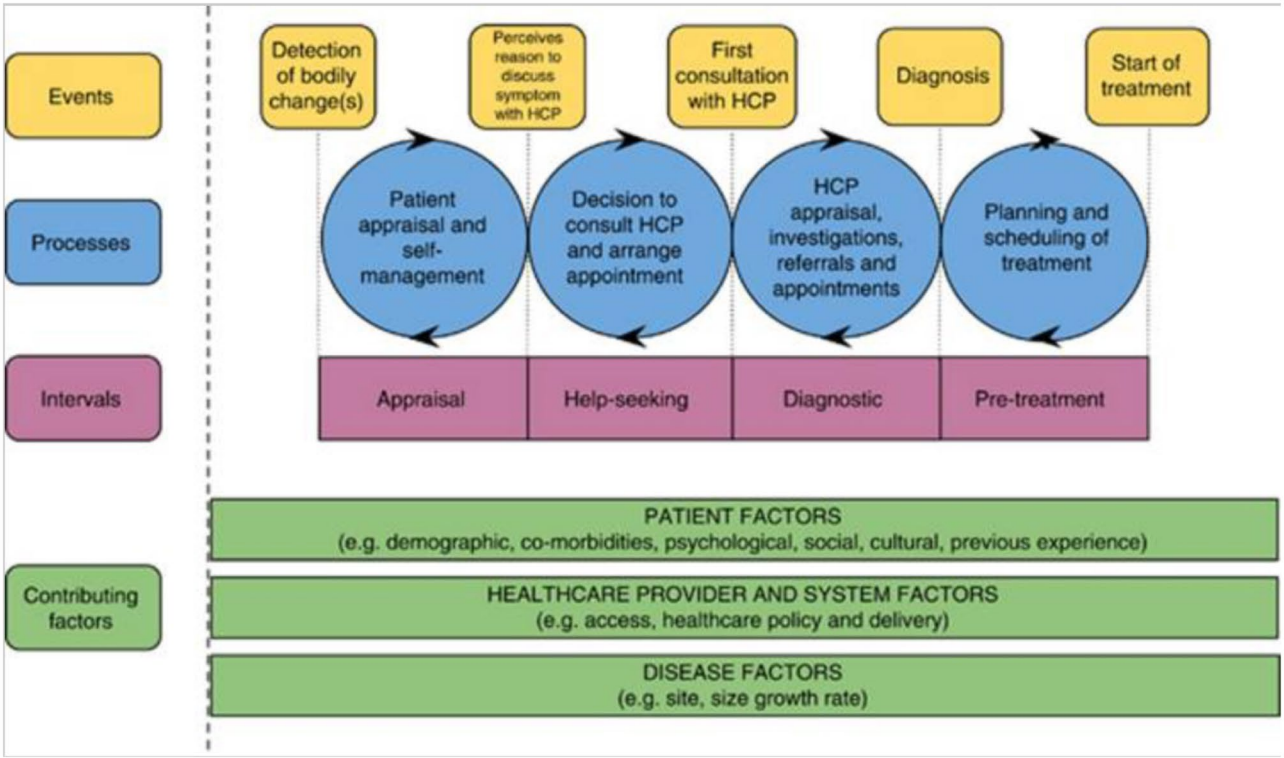

Fig. 1 The Anderson Model of total patient delay: pathway to healthcare treatment [10]

well-regarded model that proposed a standardised set of definitions (Fig. 1; Table 1) [10]. The 'Aarhus Statement', a key paper commissioned by the Department of Health England, built upon this model to define the pre-diagnostic symptom interval (PSI) as the time from onset of first symptoms to diagnosis [9].

We propose that significant delay still exists in the diagnosis of paediatric brain tumours. However, current literature is heterogeneous in the length of delay reported and associated factors. Few studies relate delay to survival. In this novel systematic review, we seek to identify patient, disease and systemic factors associated with diagnostic delay and consider its impact upon patient outcomes.

Methods

Literature search

We performed a systematic review of contemporary medical literature in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. We undertook electronic database searches of MEDLINE, Wiley Online Library, Web of Science and EMBASE (OVID) using MESH terms. We assessed sources recently published in the English language from 1st January 2010 to 5th November 2022.

Table 1 Definition of diagnostic intervals based upon the Anderson Model of total patient delay [10]

Interval	Definition
Appraisal delay	Interval between sign/symptom onset and seeking medical attention, in some studies referred to as patient delay, but more appropriately termed 'appraisal delay' by Walter et al
Physician delay	Interval from first clinical contact to referral to specialist, in some papers referred to as 'physician delay'. In many cases, there may be more than one referral to specialist services prior to the appropriate pathway for 'suspected cancer'
Diagnostic delay	Interval from specialist referral to diagnosis, often a reflection of waiting time for investigation and specialist review, termed 'diagnostic delay'. Date of diagnosis may be a heterogeneous term, which included results of imaging, biopsy or date patient was informed. Where possible, this should be defined
Pre-treatment delay	Interval from diagnosis to start of treatment, termed the 'pre-treatment delay'. This itself may be influenced by several factors such as wait for discussion at MDT, actioning of MDT outcome, and patient decision

Study inclusion

Inclusion criteria comprised (1) paediatric cohorts, defined as those under 21 years; (2) first diagnosis primary brain tumours of all grades and histology; (3) a defined diagnostic interval from symptom onset to diagnosis; (4) assessment of factors associated with diagnostic interval; and (5) reported overall patient survival outcome. We excluded studies concerned with diagnosis via genetic testing, screening or incidental diagnoses and those evaluating wider cancer cohorts lacking adequate subgroup analysis.

Two independent reviewers screened identified results for eligibility and excluded duplicates. Screening for eligibility involved title and abstract review, and where unclear, full text review. Eligible sources were obtained as full text. Identified studies were included within the qualitative analysis (Fig. 2). Data was collected by the lead reviewer using a standardised template and validated by the second reviewer. Where there was variation in reported unit of time, the unit was converted to days for uniformity. We attempted to compare intervals where definitions were analogous.

Results

Study selection

A total of 3123 studies were identified; 120 full text articles were obtained for full text review and 11 included in the narrative synthesis (Fig. 2).

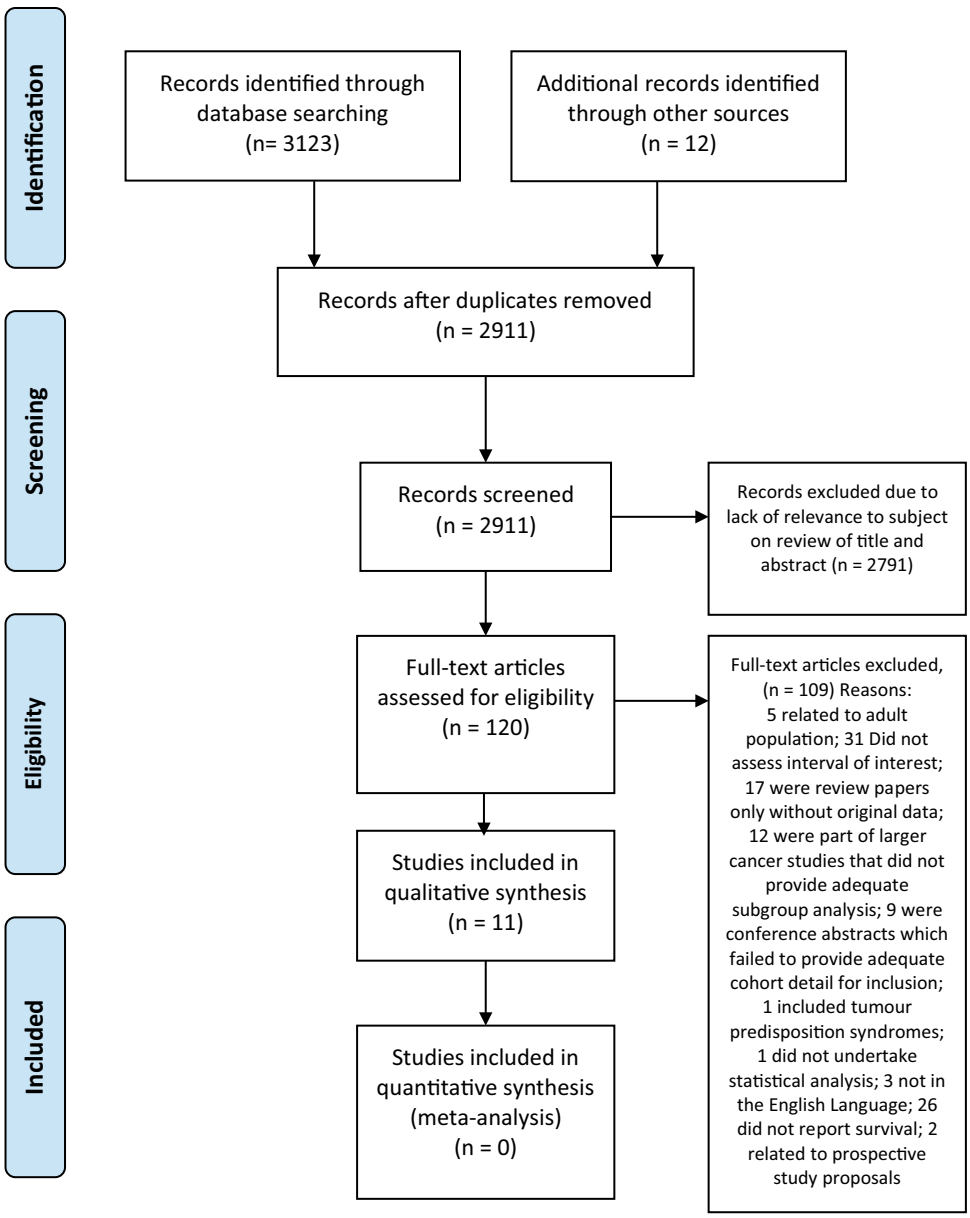

Fig. 2 PRISMA flow diagram demonstrating study selection

Table 2 Study characteristics

Study	Year	Study design	Duration (years)	Institution	Country	Tumour type	Age range (years)	Sample size
14	2015	Retrospective	10	Single centre	USA	Low-grade glioma	0.1–20.7	258
21	2020	Retrospective	4	Single centre	Mexico	All paediatric brain tumours	1 m–16	127
16	2012	Retrospective	15	Multi-centre	France	Medulloblastoma	0–15	166
20	2014	Retrospective	18	Multi-centre	Japan	All new CNS paediatric	0–14.9	127
12	2012	Prospective	5.66	Multi-centre	Switzerland	Medulloblastoma	3–18	224
15	2013	Retrospective	11	Single centre	UK	Posterior fossa tumours	0–21	66
13	2020	Prospective	13	Multi-centre	China	All paediatric CNS tumours	Mean 8.46 + 4.65	433
17	2014	Retrospective	18	Single centre	Canada	Medulloblastoma	0–17	126
19	2017	Retrospective	11	Single centre	Italy	All new paediatric CNS tumours	0–16	75
22	2021	Retrospective	11	Single centre	Japan	All new paediatric CNS tumours	0–18	154
18	2019	Retrospective	8	Single centre	China	Sellar germ cell tumours	0–18	53

Owing to heterogeneity of reported outcomes, study design and population, we were unable to identify studies suitable for quantitative synthesis and meta-analysis (Table 2). Owing to lack of quantitative data, we were unable to calculate effect size, and thus statistical heterogeneity amongst studies.

Study characteristics

Eleven studies were included within this narrative synthesis. Each varied in study design and participant characteristics (Table 2). A total of 1808 patients were included overall, with individual study cohort totals ranging from 53 to 433. All studies included retrospective data, the majority comprising single centre, observational studies based upon database and patient record searches. Two self-titled prospective studies included retrospective data collection and prospective questionnaires [12, 13].

Median age was comparable, but range varied between studies. Two studies included adolescents and young adults (aged 18–21) [14, 15]. We found several other studies within our preliminary searches which also included this subset within their analysis. A comparison of participant characteristics can be seen in Table 3.

The studies varied in tumour subtype assessed; some focused solely on specific subtype, e.g. medulloblastoma [12, 16, 17], low-grade glioma (LGG) [14] or germ cell tumours (GCTS) [18] whereas others included all types [13, 19–22]. One study focused only on posterior fossa tumours [15]. The most common tumour type overall was medulloblastoma, followed by LGG, GCTs and ependymoma.

Studies also varied in both definition and units of reporting of diagnostic intervals. Some reported only median diagnostic interval, some included interquartile ranges, whilst others presented mean and standard deviation only. Only one study provided all these metrics [15]. This heterogeneity and insufficient raw data availability prevented pooling of data

Table 3 Participant characteristics

Study	**Sample size**	**Age range (years)**	**Median age (years)**	**Gender distribution (%)**	
				Male	**Female**
14	258	0.1–20.7	7.1	50.7	49.2
21	127	1 months–16	5.5	53.5	46.5
16	166	0–15	6	72.2	27.7
20	127	0–14.9	7.2	49.6	50.4
12	224	2.9–17.5	7.5	63.8	36.2
15	66	0–21	Mean 7.5 + 4.53	47.0	53.0
13	433	*	Mean 8.46 + 4.65	59.8	40.2
17	126	0–17	7.35	*	*
19	75	0–16	7.8	60.0	40.0
22	154	0–18	6.7	57.8	42.2
18	53	0–18	10	39.6	60.4

*Data not reported

Table 4 Reported PSI amongst selected studies and association with survival

Study	Population	Cohort size	Median PSI (days)	PSI range (days)	Association with overall survival
14	**Low-grade glioma**	**258**	**63.9**	**0–3987.6**	PSI < 6 months vs. ≥ 6 months **Not significant**
21	**All**	**127**	**90**	**5–1440**	PSI < 3 months vs. 3–6 months **Not significant**
16	**Medulloblastoma**	**166**	**65**	**3–457**	**PSI > 65 days associated greater survival** ***p* = 0.02**
20	**All**	**127**	**45.6**	**0–1095**	**Not significant**
12	**Medulloblastoma**	**224**	**60.8**	**-**	PSI < 4 months vs. > 4 months **Not significant**
15	**Posterior fossa**	**66**	**43.5**	**-**	**Not significant**
13	**All**	**433**	**123**	**8–1844**	**Not significant**
17	**Medulloblastoma**	**126**	**28**	**-**	**Not significant**
19	**All**	**75**	**28**	**0–2198**	**Not significant**
22	**All**	**154**	**30.5**	**0–2280**	PSI > 30 days associated with greater survival vs. < 30 days ***p* = 0.016**
18	**Sellar germ cell tumours**	**53**	**760.4**	**-**	**Not significant**

for analysis. A range of PSI median values and individual range was evident (Table 4). The measure constituting a 'delayed' diagnosis also varied; most took a variation from their own median value to categorise 'timely' and 'delayed'.

Quality appraisal (Table 5)

Bias was assessed using a modified Newcastle–Ottawa Risk Stratification Score. We found a very high risk of bias across all studies. This appears inherent to literature published on diagnostic delay and has been previously reported [23]. Several studies were conducted through retrospective case note review, others via GP and patient questionnaires, both prone to recall bias. Many used approximations of symptom onset from parents. Hindsight may falsify the true onset of symptoms, with reports of parents subsequently recognising additional preceding clinical features in retrospect [23]. Lu et al., who collected patient outcomes via parental questionnaires, reported that a significant number of parents of deceased children declined to participate, thus leading to potential bias in survival analysis [13].

Reported pre-symptom interval

We encountered variation in the definition of intervals used to assess 'diagnostic delay'. Table 6 demonstrates the terms and intervals reported within the studies. We used 'appraisal delay' to define the time from onset of symptoms to initial presentation to a medical professional; 'physician delay' to define the point of that initial contact to obtaining a diagnosis; and 'pre-diagnostic symptom interval' (PSI), the combination of the two intervals. We utilised PSI as our primary interval of interest.

There was a range of median PSI from 28 to 760.4 days. Zhang et al.'s 2020 paper described the longest PSI, considering GCT diagnoses only [18]. The association of GCTs with a prolonged PSI has been described previously [24, 25]. Moreover, this study utilised formal tissue diagnosis as the

Table 5 Heterogeneity amongst studies of specific factors assessed for association with PSI. Orange boxes indicate factor was assessed within study analysis

Factors Assessed		14	21	16	20	12	15	13	17	19	22	18
Patient Factors	Age	■		■	■	■	■	■	■	■	■	■
	Gender	■				■	■	■				■
	Ethnicity	■										
	Parental Education/Income							■				
Disease Factors	Tumour Grade	■	■		■	■	■			■	■	
	Tumour Histology			■	■	■		■	■			
	Tumour Location	■	■		■			■		■	■	
	Disease Stage			■		■			■			■
System Factors	Site of first presentation							■			■	
	Speciality first referred to							■			■	
	No. of specialty referrals						■					

Table 6 Individual study definition of time intervals and those intervals assessed

Study	Defined interval	Onset of symptoms	Presentation to healthcare	Diagnosis	Specialist Review	Treatment	Median (days)
14	Pre-diagnosis Symptom Interval						63.9
21	Prediagnostic symptom interval						90
	Pre-Treatment Interval						13
	Global delay interval						120
16	Time to diagnosis						65
20	Prediagnostic symptomatic interval						45.6
12	Prediagnostic symptom interval						60.8
15	Pre-diagnostic symptom interval						43.5
	Parental delay						11
	Doctor's Delay						14
13	Pre-diagnostic interval						123
	Parental interval						50
	Diagnostic Interval						97
17	Pre-diagnostic Interval						28
19	Symptom Interval						28
22	Total Diagnostic Interval (TDI)						30
	Patient Interval						16
	Diagnostic Interval						4
18	Pre-diagnosis Symptom Interval						760.4*

*End point = diagnosis via biopsy at time of surgery

end point of the diagnostic interval, in contrast to radiological diagnosis. Excluding this paper as an outlier, the longest median PSI reported was 123 days. Lu et al. included a range of paediatric brain tumour diagnoses in 433 children, forming the largest study cohort within this review [13].

Secondary intervals

Only two studies reported appraisal and physician delay [13, 15]. Lu et al. found median appraisal delay to be 50 days and physician delay was 97 days [13]. In comparison, Kameda et al. found median intervals of 11 and 14 days, respectively, based upon a study of patients from the UK [15]. Both failed to demonstrate statistical significance between appraisal or physician delay and survival.

Factors associated with a prolonged PSI

a) Patient-related factors

i) Age

Seven studies assessed age as a factor in delayed diagnosis. Three demonstrated a statistically significant longer PSI in older children than in younger children [12, 14, 17]. Two of which were undertaken specifically in medulloblastoma patients. The remaining four studies failed to determine a significant relationship [15, 16, 19, 20].

ii) Gender

Five studies assessed gender [12–15, 18]. Only Kameda Smith et al. demonstrated a significantly longer PSI in females versus male children in posterior fossa tumours over an 11-year period [15].

iii) Parental education

One study assessed the potential influence of parental education, occupation and income on PSI. Lu et al. demonstrated a significantly shorter PSI in children with parents of a higher educational level. Parental age and economic status were also assessed but not associated with increased PSI [13].

Disease-related factors

i) Tumour grade

Six studies analysed tumour grade and PSI [12, 14, 15, 19, 20, 22]. Two failed to demonstrate a significant relationship [19]. In keeping with previously reported literature, the remaining four studies demonstrated statistically significantly longer PSI with lower grade lesions (World Health Organisation (WHO) grades I–II) [12, 15, 20]. Artnovic et al. reported significantly longer PSI in grade I lesions versus grade II [14].

ii) Tumour histology

Five studies were confined to a specific histological subtype [12, 14, 16–18]. Of the remaining, only one performed

subgroup analysis. Fukoka demonstrated a significant difference in PSI between histology, finding the longest PSI in patients with craniopharyngioma, followed by GCTs and LGG [20].

iii) Disease stage

Four studies assessed the relationship between PSI and metastasis at diagnosis, two focusing only on medulloblastoma [12, 16–18]. Gerber et al. demonstrated that children with advanced disease at time of diagnosis were found to have a shorter PSI than those with less advanced disease. Children with metastasis at diagnosis had a median PSI of 1 month versus those without having a median PSI of 2 months ($p = 0.094$) [12]. Ramaswarmy et al. did not find any significant difference in PSI with advanced disease stage [17]. Brasme et al. demonstrated a statistically significantly shorter median PSI in children with metastatic disease at diagnosis (31 days vs 91 days without); however, there was no significant influence on patient survival [16].

iv) Tumour location

Tumour location was not correlated to PSI in the two studies assessing this factor [19, 20].

System-related factors

Only two studies assessed the relation between PSI and system-related factors. Lu et al. analysed time to diagnosis based upon (a) location of initial attendance and (b) destination of initial referral from primary care. The authors demonstrated significantly shorter PSI in those attending tertiary versus primary care in the first instance ($p = 0.025$). The authors also found a shorter PSI in those initially referred to neurology or neurosurgery versus other specialties ($p = 0.04$). Of note, there was a high incidence of referral to alternative specialties in the first instance, for example 8.8% to gastroenterology [13]. Yamada et al. demonstrated significantly shorter PSI where a paediatrician was visited on the first consultation vs an ophthalmologist or otolaryngologist [22].

Association between PSI and outcome

a) Survival

Of the 11 studies, only one demonstrated a statistically significant relationship with outcome following adjustment for confounding factors. Yamada et al. demonstrated a superior overall survival in patients with a PSI of > 30 days versus those with PSI < 30 days [22]. A second retrospective review of 166 paediatric medulloblastoma patients demonstrated a superior survival in patients with a prolonged PSI, defined by the authors as a PSI greater than the study median of 65 days ($p = 0.02$), although this was lost following adjustment for confounding [16]. Similarly, Ramaswarmy et al. demonstrated a subtype-dependent superior overall survival with prolonged PSI [17].

b) Functional outcome

Fukoka et al. demonstrated a significantly increased incidence of persistent clinical deficits in those with a longer PSI versus those with a shorter PSI ($p = 0.03$) [20].

Brasme et al. used intelligence quotient (IQ) as an outcome measure. The authors demonstrated a significant association between increased PSI and IQ, with superior IQ associated with delay amongst survivors. However, they failed to demonstrate a significant relation between neurological disability at follow-up in survivors and prolonged PSI [16].

iii) Gross total resection

Three studies assessed relation between PSI and incidence of gross total resection and failed to find statistical significance [12, 14, 16].

Discussion

Quantifying PSI

An international standard for diagnosing paediatric tumours does not exist. UK cancer targets are available, with a national aim of investigating and counselling the patient of cancer diagnoses within 4 weeks of an initial GP referral [6]. None of the studies examined within this systematic assessed this interval.

It is important to note that the end point of PSI does not equate to the patient being informed of their diagnosis or of treatment plan creation or initiation. Thus, the reported PSI of 28–123 days may both fall short of the described UK target and ultimately be difficult to relate.

The wait for imaging, specialist review and MDT discussion to define a treatment plan may present more tangible, rate-limiting steps that can be targeted in further health policy. It is of great importance that future studies report delay in a standardised and analogous manner, allowing extrapolation of local and national guidelines.

Factors associated with PSI

Patient-related factors

The relation between PSI and age has been inconsistently reported. Several recent studies have proposed that inherent pubescent behavioural changes may contribute to an increased PSI in older children. Difficulty in distinguishing these innate changes from a pathological manifestation has been attributed to delay [12, 14]. Other authors have attributed the shorter PSI reported in younger children to more frequent medical

attendances in this age group and, as such, greater opportunity for surveillance [24–26]. Kukal et al. demonstrated a significantly shorter appraisal delay in younger children relative to older children. In contrast, older children and adolescents may be increasingly independent and less likely to visit their primary physician [26]. These findings were reflected in our review [12, 14, 17]. It is possible the link between PSI and age may be a representation of tumour epidemiology. It has been argued that younger children typically present with more aggressive disease than their adolescent counterparts, thus producing a shorter PSI. This was the finding of one study included within this review, with a subtype-dependent trend towards shorter PSI in younger children, in whom the more aggressive medulloblastoma subtype was more prevalent [18].

Overall gender did not appear to have convincing influence on PSI. The study by Kameda Smith et al. was the only one to demonstrate a significantly longer PSI in female. The authors acknowledged their female cohort appeared to have a greater distribution of lower grade lesions relative to their male counterparts, once again emphasising the importance of tumour epidemiology [15].

Only one study within our analysis assessed the impact of parental education, occupation and income upon PSI. Lu et al.'s finding of shorter PSI for children with parents of higher education levels has not been widely assessed previously and warrants further attention in future studies [13]. It highlights the importance of campaigns such as 'HeadSmart' in raising awareness [5].

Disease-related factors

It follows that patients with aggressive disease will present with a shorter PSI. This concept has been shown to exert a paradoxical effect on studies of diagnostic delay, with several studies included within this systematic review and the wider literature demonstrating advantageous survival outcome associated with a longer diagnostic interval. Conversely, higher tumour grade and more aggressive natural history have previously been shown to be associated with a shorter PSI [27–29]

In Kameda Smith et al.'s study, high tumour grade was found to be the only factor associated with a statistically significant worse outcome in terms of overall survival [15]. Fukuoka et al. reported the same conclusion in a Japanese study of 127 children with a range of tumour subtypes collected over 18 years [20].

The lack of statistical difference in diagnostic delay between tumour subtypes is likely a reflection of heterogeneity and small cohort numbers. An increased diagnostic interval in certain tumour subtypes is well reported in the literature. LGG, craniopharyngioma and GCTs present a group of lesions often associated with a longer PSI. These lesions are typically low WHO grade, slow-growing lesions presenting rarely with signs of acute hydrocephalus and mass effect versus their higher grade counterparts. Recent campaigns have made great strides towards shorter intervals, but it does appear that delayed recognition remains in this group [1].

System-related factors

Factors previously utilised to evaluate the diagnostic journey include the number of physician contacts prior to referral to the appropriate specialist, waiting time for appropriate imaging and the manner of first physician contact, e.g. primary care versus secondary care [2].

Lu et al. found PSI is significantly shorter if a child's first presentation was to tertiary care or if their initial specialist referral was to a neurologist or neurosurgeon. Within this study, only 22% of the cohort was initially referred to these specialties. Coven et al., a 2018 study excluded from our review owing to lack of survival analysis, reported increased frequency in inappropriate specialty referrals in older children versus younger, further raising the possibility that index of suspicion may reduce with increasing age [2].

Several studies have found that GP contact increases significantly in the 12 months prior to brain tumour diagnosis in children [30, 31]. Monitoring such repeat attendances may provide a means of identifying cases earlier.

The reduced PSI for those presenting initially to tertiary centres versus primary care may reflect the patient cohort presenting acutely with an underlying aggressive disease process. Dang-Tan et al. suggest prolonged PSI in countries such as the UK may relate to the role of the state-funded primary physician as gatekeeper to specialist referral and imaging, adding another factor to the diagnostic process. This contrasts to privatised health care systems wherein direct access to specialist care is readily available [32].

Key intervals in the diagnostic pathway such as wait for imaging, for specialist review or for surgery were not assessed in any study included within this review. In the context of increasing healthcare demands, the wait for diagnostic imaging is likely to remain a key target for improvement. Imaging availability for infants and young children is perennially impeded by frequent need for general anaesthesia and day case admission. Future studies assessing these factors would be of great benefit.

PSI and patient outcome

Overall survival

Our systematic review has failed to demonstrate that prolonged diagnostic interval results in an inferior overall survival for children with new brain tumour diagnoses. Only one study included in our synthesis demonstrated a statistically significant relationship between diagnostic delay and survival. Yamada and colleagues in fact demonstrated superior survival with prolonged PSI [22]. Kukal et al. also demonstrated a higher overall survival and progression-free survival in patients with the longest PSI [26].

This seemingly paradoxical relationship has been reported in other studies on the topic and can be explained by the indolent natural history seen in lower grade lesions, when compared to aggressive, rapidly progressive high-grade tumours. This finding, referred to as 'the waiting time paradox', has also been reported in adult brain tumour studies [26–28].

Functional outcome

Few studies assessed the potential impact of prolonged PSI on neurological disability. Only one assessed IQ whilst none assessed quality of life [16]. We hypothesise that the longer a lesion is permitted to produce neurological deficits, the less likely that neurological deficit will resolve. Preventing such irreversible neurological deficit forms a key rationale for the drive to promptly diagnose and treat such lesions. From the limited assessment observed within the studies assessed, this hypothesis remains to be corroborated.

Gross total resection

Diagnostic delay has been proposed to contribute to missed opportunity for complete surgical resection. It is of interest that of the three studies that assessed this relationship, none demonstrated a statistically significant relationship. These findings are important given the emphasis placed upon gross total resection and its impact on prognosis [19, 28, 33, 34].

Limitations

We encountered significant study heterogeneity in not only outcomes but also population and methodology. Launay et al. have published a 'critical criteria checklist' for such articles [35]. Future studies would benefit by consideration of such criteria. Small cohort numbers underpower individual studies, with numbers of tumour subtypes, grade or location smaller still, weakening any subgroup analysis. Larger cohorts for population-based studies analysed by tumour type would be of benefit, for example via national, multi-centre collaboration. Many studies identified within preliminary searches failed to assess outcome. Future studies assessing diagnostic delay must assess outcome measures, be it overall survival, functional, neurological or quality of life measures in order to inform clinical practice.

Conclusion

The relationship between diagnostic delay and survival in this population is complex. Increasingly, it appears PSI is dictated largely by tumour biology and as such may not be truly representative for all tumour types. Our results contradict the hypothesis that longer PSI is associated with an inferior survival. Moreover, it does not appear that a prolonged PSI is associated with inferior gross total resection, a key prognostic indicator in this population.

It is important to acknowledge that PSI is but one factor in an often-complex patient journey. Whilst the relationship between PSI and patient survival may be inherently confounded by the underlying natural history of the tumour, it remains to be seen if we can identify a modifiable rate-limiting factor for improving outcome.

Due to lack of high-quality, focused studies, we were unable to determine the influence of waiting times for imaging, specialist review, multi-disciplinary team (MDT) discussion and initiation of treatment on patient outcomes. It would be of great interest to evaluate these in future studies.

The quality of life amongst those with a longer diagnostic interval would be a likely revealing hidden cost. Relation of a delayed diagnosis to neurological deficits and the influence of a delayed diagnosis on parental and child mental health are important factors to consider.

Clinician suspicion and parental vigilance remain factors of paramount importance in achieving prompt diagnoses in paediatric patients with brain tumours. We propose that attention should be focussed on systematic factors and production of high-quality studies on diagnostic delay in the future to identify elements of the diagnostic pathway that will improve patient outcomes.

Author contribution KK and CC contributed to the study conception and design. Material preparation, data collection and analysis were performed by KK and HS. The first draft of the manuscript was written by KK and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Not required

Conflict of interest None declared by the authors.

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