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The Utility of Routine Surveillance Screening with Magnetic Resonance Imaging (MRI) to Detect Tumor Recurrence / Progression in Children with High-Grade Central Nervous System (CNS) Tumors: A Systematic Review

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ABSTRACT

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Background: Surveillance Magnetic Resonance Imaging (MRI) is routinely used to detect recurrence in children with high-grade central nervous system (CNS) tumors, although no consensus has been reached regarding its effectiveness and whether earlier detection is associated with improved patient outcomes. This review aimed to evaluate this practice and any associated benefits and harms. **Methods**: Systematic searches for relevant studies were undertaken in a number of databases, including MEDLINE and EMBASE, from 1985 to August 2018. Study selection and data extraction was undertaken independently by two reviewers. Due to heterogeneity between studies, no pooling of data was undertaken. Reporting followed PRISMA guidelines. **Results:** No comparative studies were identified. Three retrospective observational studies involving 306 patients were reviewed. All had high risk of bias by virtue of study design. Two studies reported outcomes by symptomatic status - both recurrence rates and overall survival for asymptomatic patients were comparable to those for clinically symptomatic patients. No quality of life outcomes were reported. **Conclusion:** There is a paucity of evidence to guide clinical practice as to the effectiveness

of MRI surveillance in paediatric patients with high grade CNS tumors. These studies do not clearly demonstrate benefit or harm for the practice. With more research needed, there is a role for researchers to build into future trials data collection on surveillance imaging to give more information for the assessment of imaging frequency and duration in asymptomatic patients. This is an important question, not only to clinicians and patients and their families but also from a health service resource perspective.

Introduction

Paediatric high-grade central nervous system (CNS) tumors are fast-growing, malignant tumors with metastatic potential and are commonly associated with poor prognosis even after multi-modal treatment. Generally classified by the World Health Organization (WHO) as either grade III or IV tumors, they include glial (anaplastic astrocytoma and glioblastoma multiforme), ependymal (ependymoma, both WHO grade II and III) and embryonal (medulloblastoma and tumors previously known as primitive neuroectodermal tumors (PNET)) tumors, as well as brainstem tumors (diffuse pontine glioma (DIPG)) atypical teratoid/rhabdoid tumor (AT/RT) and pineoblastoma. Many children with high-grade CNS tumors will go on to experience recurrence or progression and the likelihood of this will depend on the histology and location of their first tumor, as well as treatments given.[1,2]

In recent years, Magnetic Resonance Imaging (MRI) has become the predominant imaging tool in the management of children with high-grade CNS tumors. The rationale behind routine imaging, or surveillance, is that recurrence or progressive disease detected at an earlier stage may be more responsive to treatment and benefit from a wider range of treatment options than disease diagnosed at a later stage from clinical signs and symptoms. However, no consensus has been reached as to whether this leads to improved outcomes for patients and their families.

The objectives of this review were therefore to:

1. assess the diagnostic utility of surveillance MRI in detecting tumor recurrence prior to the emergence of new clinical signs and symptoms compared to the nonroutine use of MRI upon symptomatic presentation, and assess whether this practice translates to measurable improvements in clinical outcomes;

2. consider the effect of differing screening intervals on the diagnostic utility of surveillance MRI and determine the optimal duration of imaging after initial diagnosis; and
3. identify any gaps and methodological weaknesses in the current evidence base and make recommendations to inform the design and analysis of future studies.

The authors have also undertaken a systematic review on the effectiveness of surveillance MRI in paediatric low-grade tumors, which forms a companion piece to this review paper.[3]

Methods

Standard systematic review methodology was employed and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[4] A detailed account of the methodology employed in this review can be found in the published protocol, which is also registered with PROSPERO (CRD42016036802).[5] A summary of the methods are described below.

Search strategy

This review formed part of a wider NIHR-funded work programme of systematic reviews aimed at assessing the effects of different interventions for the treatment of paediatric CNS tumors and therefore searches were not restricted to studies concerned solely with surveillance imaging in children with high-grade tumors. Searches for published studies from 1985 to August 2018 were undertaken in several databases, including MEDLINE and EMBASE. (See Supplementary File S1). No language, publication restrictions or study design filters were applied.

Study selection

The following inclusion and exclusion criteria were applied:

Population*:* Children and young adults (up to age 25 years) with diagnoses of any type of high-grade CNS tumor who were asymptomatic at the time of study recruitment. Given that children undergoing surveillance may have some neurologic sequelae from their tumor and/or its treatment, it would be more accurate to characterise patients as exhibiting no new, stable or improved neurological signs or symptoms.

Interventions**:** Routine or surveillance MRI. Studies employing computed tomography (CT) as the sole surveillance imaging modality were excluded.

Outcome Measures: Recurrence rates (by study, tumor type, location and extent of resection), diagnostic yield of imaging, timing of recurrence, change in patient management post-recurrence, overall survival (OS), surrogate survival measures (e.g. recurrence-free survival (RFS), progression-free survival (PFS)) and quality of survival. Studies reporting outcomes from aggregated CT and MRI scans were excluded.

Study designs**:** As randomized controlled trials (RCTs) and nonrandomized comparative studies were initially sought but not identified, the review was extended to include observational studies such as case series.

Study selection was undertaken by two independent reviewers, with disagreements resolved by discussion.

Data extraction and risk of bias assessment

Data, extracted by one reviewer and checked by a second, were recorded on a standardised proforma developed in Microsoft Word (See Supplementary File S2). Risk of bias was assessed at the study level by two reviewers using a six-point tool devised by the Centre for Reviews and Dissemination (York; CRD)[6] designed to assess bias in case series studies.

Statistical analysis

Due to the design of the included studies and the heterogeneity of outcomes reported, only a descriptive analysis was undertaken.

Results

Quantity and description of included studies

From the electronic database searches, 28 potentially relevant publications were identified with an additional 13 publications identified from citation-checking. On full text examination, 38 were excluded including 11 studies which employed both CT and MRI as surveillance imaging modalities but failed to report results separately for MRI. (See Supplementary File S3). No RCTs or prospective comparative studies were identified. Three retrospective case series studies[7-9] were included in the review. (See Figure 1).

The three studies were conducted between 2001 and 2014 and undertaken at single centre institutions. Two studies[8,9] included patients with high-grade tumors only, with one[7] including a mix of low- and high-grade tumor patients. (See Table 1).

Quality of the research

Studies were clinically heterogeneous with study populations varying in terms of both tumor type and disease severity. Study samples were small but patients appeared to be representative of the target population, although it was unclear whether patients were at a similar timepoint in the disease progression. Inclusion and exclusion criteria for each study were explicitly stated. Generally details of previous treatments were not reported. (See Supplementary File S4). There was also variability in terms of reporting and defining of outcomes. The terms 'recurrence' and 'progression' were defined in all three studies, although only two reported recurrences as 'symptomatic' and 'asymptomatic' and defined these terms.[7,9] All three studies reported OS, although only Kornreich[8] defined the term. (See Table S5). This was also the only study to report PFS. Korones[7] did not report average duration of follow-up.

Included studies

Korones (2001)[7]

Korones[7] was a mixed tumor grade study with 112 children at study commencement. Patient details were provided only for the 46 patients who went on to experience recurrence/progression. Of these, 33 had high-grade tumors. Eight tumor types were

included. The median age of these patients at recurrence was six years (range 0.25 – 21) although this was not reported by tumor type.

All patients underwent surgery as the primary treatment, although this was not further specified by extent of resection (i.e., gross total resection (GTR) versus sub-total resection (STR)). At the commencement of surveillance imaging, none of the patients had relapsed disease.

With respect to imaging frequency, patients received a median of one scan every 2.5 months (range 1/1 – 1/6.7 months) irrespective of whether they were symptomatic or asymptomatic at recurrence. Frequency of scanning was not reported by tumor type.

As only data on recurrent patients was reported, it was not possible to calculate the recurrence rate for the 33 high-grade tumor patients as a whole, nor by tumor type. The rate of recurrence/progression by symptomatic status was reported, with 17 patients (52%) asymptomatic at recurrence. Recurrence by symptomatic status was also reported by tumor type, with asymptomatic and symptomatic recurrences comparable in number, although the numbers in each category were very small (ranging from 1-6). (See Table 2). Recurrence by extent of resection was not reported.

The diagnostic yield of imaging for all seventeen asymptomatic patients was 4.4%, i.e., one asymptomatic recurrence detected every 23 MRI scans. (See Table 2). With respect to CPC, GCT and AT/RT, there were two asymptomatic recurrences among these tumor types and the diagnostic yield of imaging was 6.5%.

Median time to recurrence from initial diagnosis for all 33 patients was 0.75 years with no significant difference in median time to recurrence between symptomatic and asymptomatic patients at recurrence (0.66 and 0.77 years respectively). Median time to recurrence was not reported by individual tumor type, nor by extent of resection.

Information regarding local therapy received following recurrence/progression was provided for 26 patients (79%), with eight of 14 asymptomatic patients (57%) undergoing local therapy (surgery with or without stereotactic radiosurgery) compared to only three of 12 symptomatic patients (25%) ($p = 0.13$). Again, change in patient management was not reported by tumor type.

Overall survival from recurrence for all 33 patients was reported but only by symptomatic status at recurrence, with median OS for the 17 asymptomatic patients (0.58 years) marginally and nonstatistically significantly greater (p=0.25) than that for the 16 symptomatic patients (0.42 years). Median OS was not reported by tumor type.

Kornreich (2005)[8]

Kornreich[8] was a retrospective case series study looking at the role of surveillance MRI in the management of 15 paediatric patients with DIPG. While the frequency of imaging was not reported, the mean number of MRI scans per patient was six. Thirteen patients (87%) experienced tumor progression while two patients remained stable. Symptomatic status of patients at progression was not reported.

Median PFS was 0.83 years, ranging from 0 months (in 4 patients who deteriorated immediately from diagnosis without any prior period of stability) to nine years. Treatment

(radiotherapy and/or chemotherapy) was planned and not consequent to changes in scans or recurrence. Median OS was 1.67 years, with three patients (20%) alive at the time of reporting.

Perreault (2014)[9]

Perreault[9] was a retrospective case series study which sought to assess the benefits of surveillance MRI in a cohort of 258 high-grade tumor patients. There were seven tumor types included. (See Table 1). All patients underwent surgery as the primary treatment although this was not further specified by extent of resection. At commencement of surveillance imaging, none of the patients had relapsed disease.

While frequency of scanning was not reported, the median number of MRI scans per patient across all tumor types was 13, ten of the brain and three spinal. (See Table 3). The interval since last MRI for symptomatic patients was not longer for symptomatic compared to asymptomatic patients (mean 3.9 versus 4.8 months).

Rates of recurrence/progression were also reported by symptomatic status. (See Table 3). With respect to first recurrences (n=113), there was a slight predominance of asymptomatic (46%) compared to symptomatic recurrences (42%), whereas for subsequent recurrences (n=125) the converse was the case (29% versus 58%). Recurrences (both first and subsequent) by symptomatic status were also reported by tumor type where, in the case of medulloblastoma and ependymoma, this trend continued with the majority of first recurrences asymptomatic and second symptomatic. Conversely, for sPNET, the majority of first recurrences were symptomatic and second asymptomatic. For HGG, the majority of both first and second recurrences were symptomatic. For the remaining tumor types (GCT, AT/RT and

pineoblastoma), the number of recurrences was so small that caution should be exercised when comparing recurrences by symptomatic status (most notably AT/RT, with 100% of first recurrences asymptomatic based on only four patients). Recurrences among glioma patients were more frequently symptomatic compared to those patients with other tumor types (68 versus 38 % respectively; p=0.003). The rate of recurrence by extent of resection was not reported.

A breakdown of MRI scans by both tumor type and site of imaging was reported, with diagnostic yield across all tumor types of 8.3% for brain recurrence only (range 2.1% to 21.6%), 3.8% for combined brain-spine recurrence (range 1.6% to 19.7%) and 0.9% for spine recurrence only (range 0.7% to 4.9%). (See Table 3).

Median time to recurrence from initial diagnosis was 1 year, although it is unclear whether this relates to first or all recurrences. Median time to recurrence by tumor type was reported but, again, it is unclear if this relates to first or all recurrences. (See Table 3). No significant difference in median time to recurrence was reported between symptomatic and asymptomatic patients at recurrence (1.0 and 0.92 years respectively; $p>0.8$). The time by which greater than 90% of recurrences had occurred for each individual tumor type was also reported. (See Table 3). Median time to recurrence by extent of resection was not reported.

Change in patient management following first recurrence was reported for 93% of patients, with 59% of patients undergoing new treatments, 11% continuing with existing treatment, 16% scheduled for palliative care and 7% undergoing closer interval surveillance MRI. New treatments consisted of chemotherapy (22% standard dose and 4% high dose with stem cell support), radiotherapy (6%), radiosurgery (2%), surgery (5%) and unspecified multi-modal

therapy (20%). Change in patient management post-recurrence by tumor type was not reported.

There was no significant difference ($p > 0.3$) in median OS from recurrence between symptomatic and asymptomatic patients (1.92 years and 2.25 years respectively). Median OS by tumor type was not reported.

Discussion

This systematic review is one of a series evaluating treatments for children with CNS tumors. Underpinning the reviews was consultation with clinical experts and a Patient and Public Involvement (PPI) group, consisting of mothers of children with CNS tumors. The PPI group in particular expressed concerns about over-scanning, especially in situations where scanning is no longer able to influence prognosis as in the case of patients for which nothing further can be clinically done. As well as the unknown risks associated with repeated administration of contrast materials such as Gadolinium,[10] anaesthesia and sedatives, the PPI group spoke of what has come to be termed 'scanxiety', i.e. an overwhelming feeling of stress experienced by both patient and family around the time of scanning. As one parent put it "At times, it seems like life and all its decisions revolve around scanning, which serves as a constant reminder of the cancer and acts as an obstacle to resuming normal behaviour."

Although the use of surveillance MRI is standard practice throughout the developed world in the management of children with high-grade CNS tumors, this systematic review did not identify any RCTs evaluating this intervention. After excluding 11 high-grade tumor surveillance imaging studies which employed both CT and MRI but did not report results separately by imaging modality,[11-21] the review included three retrospective, single arm

studies (n=306 patients) with MRI employed as the sole imaging modality. It could be argued that in excluding studies employing CT imaging, the review has lost valuable data on surveillance. However, the reason for focussing on MRI, other than its superior sensitivity, is that MRI studies are more recent than CT studies and therefore encompass an era of improved survival and greater salvageability of patients due to improved treatments.

The findings of the review were mixed. Korones[7] concluded that "asymptomatic recurrences were detected in only a small proportion of surveillance scans and had no impact on survival in children with high-grade tumors." Kornreich[8] reported on 15 patients with DIPG and compared the findings of 51 surveillance scans with those from clinical examination and reported a high degree of concordance (87%), suggesting that for DIPG, surveillance MRI is providing little information over and above that conveyed by clinical symptoms and signs and therefore its utility may be limited. Ultimately, surveillance imaging did not affect the treatment given, nor the outcome. Based on this evidence, it could be argued, albeit tentatively, that certain tumor types may be more amenable to surveillance MRI than others and that for aggressive tumors such as DIPG, where often any period of clinical stability is extremely limited, there is a very short window of opportunity for surveillance imaging to exploit. In support of this, Kornreich[8] reported four patients with zero time to progression. However, with other, less aggressive high-grade tumor types, the use of MRI surveillance may be of value. For example, with Perreault[9] asymptomatic recurrence rates were higher for ependymoma and medulloblastoma compared to other tumor types, suggesting that surveillance might potentially be beneficial to these patients, although in this study asymptomatic patients across all tumor types did not benefit from improved overall survival compared to symptomatic patients. Unfortunately, the potential for bias within case series is considerable and therefore conclusions from this review are tentative and should be viewed with extreme caution.

There were several reporting problems that made comparison across the studies problematic. Korones failed to report frequency of MRI imaging by tumor grade or type thereby rendering a cross-study comparison of the effect of differing imaging schedules on the rate of asymptomatic recurrence for different tumor types impossible.[7] Similarly, Kornreich[8] did not report patients by symptomatic status at time of progression. Only Perreault[9] reported patients and recurrences by tumor type and symptomatic status, enabling observations to be drawn which could potentially inform the design of future trials. However, it is important to appreciate that the data analysed in these studies were acquired for clinical purposes for which assessment of surveillance imaging protocols was not an objective.

The initial aim of this review was to assess the effectiveness of surveillance MRI. RCTs were required to do this but as none were found, focus was switched to finding studies that were specifically conducted to describe surveillance scanning. With just three studies meeting the inclusion criteria, one criticism of this review which emerged from the peer review process was that the co-operative trials should have been hand-searched for information on surveillance. This does raise an interesting point about the best way to systematically review paediatric oncology trials. Systematic reviewing (especially employing Cochrane methodology) was developed with single question trials involving more common diseases in mind, i.e. A versus B, whereas paediatric oncology trials tend to be co-operative, multi-modal trials that attempt to answer a variety of questions within a single trial due to the rarity of the diseases. In response to the peer review feedback, a search of co-operative trials in medulloblastoma was undertaken to determine whether there was data within these trials to inform the review question. Of 27 trials, surveillance MRI scanning intervals appeared to be arbitrary and variable, with few reasons given for the surveillance schedules. (See Supplementary File S6). Only one study, not identified in our systematic review searches

likely due to indexing, evaluated the number of patients who had relapse detected through surveillance MRI compared to symptom-based relapse.[22] (This study reported that 45 relapses were detected on surveillance MRI, with 20 detected from symptoms alone. Of these, patients detected from symptoms had a significantly shorter survival post-relapse than those detected by surveillance MRI ($p<0.01$), although OS post-primary diagnosis was not statistically significantly different. This could be due to lead time bias or that patients in the symptomatic relapse group possibly have more aggressive tumors). Finding the evidence in a systematic way, from identifying the relevant publications to finding the information within the trial publications (often results are written into the discussions) can be challenging in these large co-operative trials. In future, we recommend that systematic reviewers consider hand-searching relevant co-operative trials, whilst bearing in mind that the main aim of these trials might differ from that of the systematic review. We also urge authors of co-operative trials to improve the transparency of their publications, especially with respect to database indexing as well as signposting and organization of information within the papers.

The paucity of data evidenced in this review may be due to the complexity of surveillance in these patients, with frequency of monitoring depending on tumor type, disease status (newly diagnosed, resistant or relapsed), extent of metastatic spread and previous treatments. Other factors such as pseudo-progression and radiation necrosis can also complicate the interpretation of scans, making it a difficult area to investigate. However, there is a need to examine this question further in order to guide clinicians in developing optimal evidence-based surveillance strategies, to help parents and children understand the need for surveillance and to optimise the use of health service resources. There is a role for researchers to build into future, large co-operative trials methodology that investigates the role of surveillance MRI or at the very minimum, collects and reports data on the trial surveillance

MRI practice, as well as incorporating quality of life data collection, particularly regarding anxiety around surveillance and the reassurance that it may also afford.

Conclusion

Only three retrospective observational studies with a high risk of bias were identified to guide clinical practice of surveillance MRI for children with high-grade CNS tumors.[7-9] These studies do not clearly demonstrate benefit or harm for this practice, nor do they define methods or intervals for maximal effectiveness. To resolve this, more research is needed with the ultimate endpoints of surveillance relating to survival and quality of life, as opposed to surrogate outcomes such as the detection of tumor growth. As most of the patients within this group are treated within the context of a co-operative clinical trial, this research could be built into trial protocols for very little extra investment. It is an important question, not only to clinicians and patients and their families but also as a health service resource question.

Figure 1: PRISMA diagram of flow of studies through the selection process

Supplementary file S1: Search strategy

Supplementary file S2: Data extraction and quality assessment proforma

Supplementary file S3: List of excluded studies

Supplementary file S4: Quality assessment of included studies

Supplementary file S5: Definitions of recurrence / progression and symptomatic / asymptomatic provided by study authors

Supplementary file S6: MRI imaging schedules in co-operative trials in paediatric medulloblastoma

Compliance with ethical standards

Disclosure of potential conflicts of interest: The authors declare that they have no conflict of interest.

Informed consent: Not required for this type of study (i.e. systematic review).

Ethical approval: Not required for this type of study (i.e. systematic review).

Research involving Human Participants and/or animals: This article does not contain any studies with human participants or animals performed by any of the authors.

Authors' contributions

SPS conceived and designed the study and wrote the article. CM conceived and designed the study and read and commented on the article. SB, BP, ME, RP conceived the study concept, provided clinical input and read and commented on the article. AP, SA, SW and PRK provided clinical input and read and commented on the article. KW conceived and designed the study, provided methodological and statistical input and read and commented on the article. JSW conceived and designed the study, revised the article and is the guarantor of the review. All authors read and approved the final manuscript.

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