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WHOLE BODY MAGNETIC RESONANCE IMAGING ON THE DIAGNOSIS OF METASTASIS IN CHILDREN AND ADOLESCENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Porto Alegre,
2019

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Whole body magnetic resonance imaging on the diagnosis of metastasis in children and adolescents: a systematic review and meta-analysis.

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Tese de Doutorado apresentada ao curso de Pós-Graduação em Medicina/Pediatria e Saúde da Criança da Pontifícia Universidade Católica do Rio Grande do Sul, como parte dos requisitos necessários à obtenção do título de Doutora em Pediatria e Saúde da Criança

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RESUMO

Introdução: A Ressonância magnética de corpo inteiro (WB-MRI) trouxe a vantagem de uma avaliação abrangente de pacientes pediátricos sem os riscos inerentes à radiação ionizante normalmente presente em outros métodos convencionais de imagem. No entanto, a acurácia da RM-WB para o diagnóstico de metástase em crianças e adolescentes não foi estabelecida.

Objetivo: Avaliar a acurácia diagnóstica da BM-RM no diagnóstico de metástase em crianças e adolescentes.

Materiais e métodos: Foram pesquisados os seguintes bancos de dados eletrônicos: MEDLINE, EMBASE, Cochrane Controlled Trials Register, Scientific Electronic Library Online, Literatura Latino-Americana do Caribe em Ciências da Saúde, Índice Cumulativo de Enfermagem e Literatura Aliada em Saúde, Web of Science e www.clinicaltrials .gov. A meta-análise foi realizada de acordo com as recomendações do manual Cochrane. Uma análise de sensibilidade foi realizada para avaliar a robustez de nossas análises, excluindo estudos da análise geral de alta heterogeneidade.

Resultados: Os estudos selecionados incluíram 1055 locais de metástase em 68 pacientes com idade variando de sete meses a 18 anos. As estimativas resumidas obtidas a partir da análise de WB-MRI foram sensibilidade de 0,965 (IC 95% 0,934 a 0,984, I^2 = 0%), com especificidade de 0,878 (IC 95% 0,853 a 0,899, I^2 = 99,3%). Quando o estudo com baixa robustez foi excluído, a heterogeneidade diminuiu, de ambos os testes, para zero.

Conclusão: A ressonância magnética de corpo inteiro tem boa acurácia para o diagnóstico de metástase em crianças e adolescentes, e poderia fornecer um método alternativo não ionizante para o estadiamento da doença.

Palavras Chaves: Ressonância magnética de corpo inteiro (RM de corpo inteiro); PET/CT com FDG; Metástase; Crianças; Adolescentes.

ABSTRACT

Background: Whole-body magnetic resonance imaging (WB-MRI) has brought the advantage of a comprehensive evaluation of pediatric patients without the risks inherent to ionizing radiation usually present in other conventional imaging methods. However, consensus regarding WB-MRI accuracy for the diagnosis of metastasis in children and adolescents is still lacking.

Objective: To evaluate the diagnostic accuracy of WB-MRI in the diagnosis of metastasis in children and adolescents.

Materials and methods: The following electronic databases were searched: MEDLINE, EMBASE, The Cochrane Controlled Trials Register, Scientific Electronic Library Online, Latin American Caribbean Health Sciences Literature, Cumulative Index to Nursing and Allied Health Literature, Web of Science, and www.clinicaltrials.gov. Meta-analysis was performed according to the recommendations of the Cochrane handbook. All studies included children and adolescents with histopathological proof of the original tumor. All patients underwent a reference standard. Different reference standards were used, including clinical outcomes, biopsy, iliac crest biopsy, focal imaging methods follow-up and expert panel review, and the gold standard of each patient was established. Using the stablished gold standard, sensitivity, specificity and positive predictive values were calculated for eath technique. Any study have been used endovenous contrast.

Results: The selected studies included 118 patients with age ranged from seven months to 19 years. The summary estimates obtained from analysis of WB-MRI were sensitivity of 0,964 (95%CI 0,944 to 0.978, I^2= 0%) with specificity of 0.902 (95%CI 0.882 to 0.919, I^2= 98,4%) and AUC=0.991. When the study with low robustness was excluded, heterogeneity decreased, of both tests, to zero.

Conclusion: Whole Body Magnetic Resonance Imaging has a good accuracy for the diagnosis of metastasis in children and adolescents and could potentially provide a safer nonionizing alternative method for staging disease.

Keywords: whole body MRI (WB-MRI); FDG-PET/TC PET/TC; metastasis; children; adolescents.

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1 INTRODUCTION

Cancer has been considering an important risk factor of natural death in the pediatric populations. However, when a cancer is diagnosed in its early stages the cure rate can be high.(1) Several imaging tools are used to describe the extent of local and distant disease. If possible, imaging techniques must be fast, provide high quality images, have a low radiation, and provide clinically important information. (1-3)

Whole-body magnetic resonance imaging (WB-MRI) is a noninvasive imaging method that can be used to diagnose, stage, and evaluate therapeutic response in oncology. WB-MRI has high soft-tissue contrast and spatial resolution and absence of radiation exposure. The wide anatomical coverage provided by WB-MRI is of appeal for PET/CT, are more often routinely employed. Effectiveness has been shown in staging already diagnosed malignancies as well as screening in patients with genetic cancer predispositions.(1, 4-7) The practice and demand for this tool in oncology are increasing because of technologic innovations and as a result of the increase of evidences showing its validation in the clinical practices. (1, 4-7)

Exposure to ionizing radiation is a major concern in pediatric patients with cancer. However, imaging methods that use ionizing radiation sources, such as X-ray, computed tomography, bone scintigraphy, and PET/CT, are often routinely employed.(1-3). The awareness of the potential health risks from radiation exposure, especially in the pediatric population, explains the preferential use of techniques which do not carry these risks, such as ultrasound and WB-MRI. With recent improvements in magnetic resonance imaging hardware and software and resultant dramatically reduced scan times, imaging of the whole body with WB-MRI has become a much more practical technique in children(1, 2, 4)

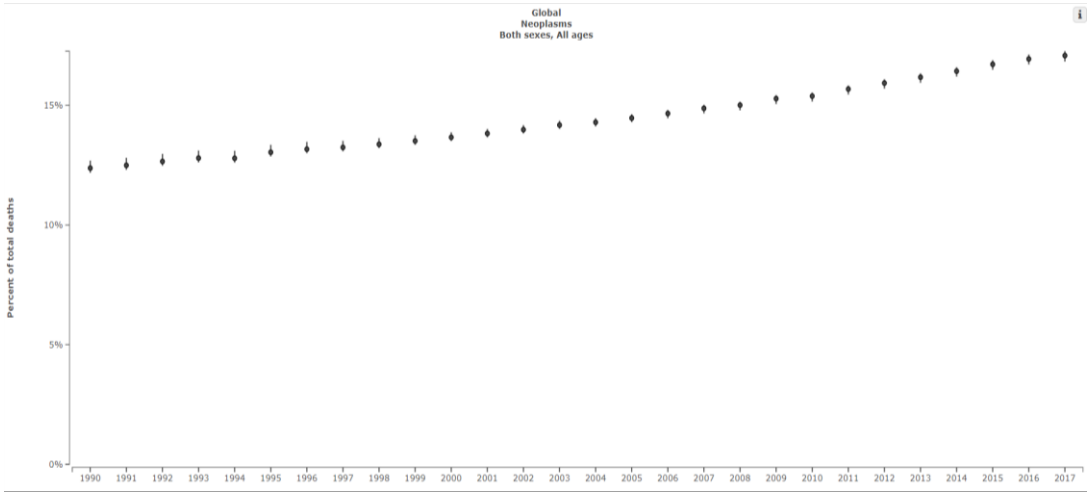
Evidence in specific scenarios suggests that WB-MRI is preferable to PET-CT for assessing metastatic disease. The latter provides a high level of soft tissue and skeletal detail and is radiation free, whilst PETCT, CT or other scintigraphy methods are not. (1) However, few studies have been conducted to evaluate the use of MRI for assessment of metastatic spread in children and adolescentes. (1, 4-7)

The objective of this systematic review and meta-analysis was to evaluate the diagnostic accuracy of WB-MRI in metastasis diagnosis of children and adolescents.

2 SCIENTIFIC FOUNDATION

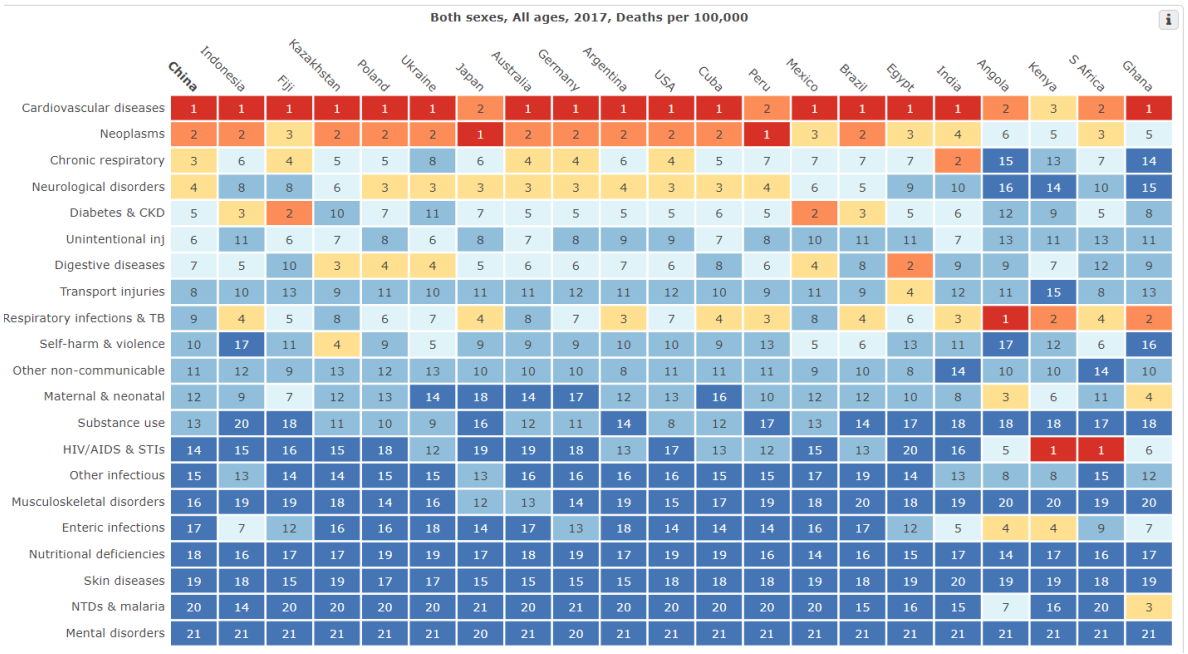
2.1 CANCER

Cancer is one of the major causes of global morbidity and mortality. Recent estimative showed that these numbers are expected to rise, with a projected 22 million new cancer cases and 13 million cancer-related deaths occurring annually by 2030.(8) The Global Burden of Disease (GBD) data strengthens this projection. The graph below demonstrates the growth in the percentage of cases of neoplasms. (Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Causes of Death and Nonfatal Causes Mapped to ICD Codes. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018).



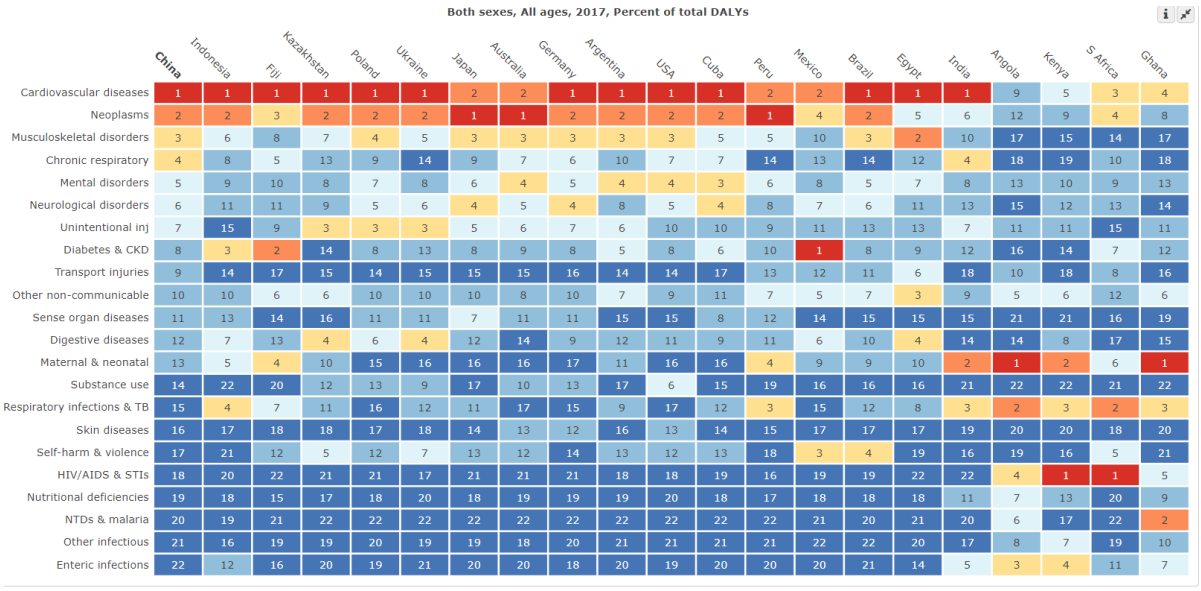
Fonte: Global Burn of Diseases

In the GDB data, it is also possible to detect that the cancer is between the first and third cause of death and Disability Adjusted Life Years (DALYS) in most of the investigated countries. In Brazil, the neoplasia's are second cause of DALYS. (Global Burden of Disease Collaborative Network) Global Burden of Disease Study 2017 (GBD 2017) Causes of Death and Nonfatal Causes Mapped to ICD Codes. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018).



	China	Indonesia	Fiji	Kazakhstan	Poland	Ukraine	Japan	Australia	Germany	Argentina	USA	Cuba	Peru	Mexico	Brazil	Egypt	India	Angola	Kenya	S Africa	Ghana
Cardiovascular diseases	1	1	1	1	1	1	2	1	1	1	1	1	2	1	1	1	1	2	3	2	1
Neoplasms	2	2	3	2	2	2	1	2	2	2	2	2	1	3	2	3	4	6	5	3	5
Chronic respiratory	3	6	4	5	5	8	6	4	4	6	4	5	7	7	7	7	2	15	13	7	14
Neurological disorders	4	8	8	6	3	3	3	3	3	4	3	3	4	6	5	9	10	16	14	10	15
Diabetes & CKD	5	3	2	10	7	11	7	5	5	5	5	6	5	2	3	5	6	12	9	5	8
Unintentional inj	6	11	6	7	8	6	8	7	8	9	9	7	8	10	11	11	7	13	11	13	11
Digestive diseases	7	5	10	3	4	4	5	6	6	7	6	8	6	4	8	2	9	9	7	12	9
Transport injuries	8	10	13	9	11	10	11	11	12	11	12	10	9	11	9	4	12	11	15	8	13
Respiratory infections & TB	9	4	5	8	6	7	4	8	7	3	7	4	3	8	4	6	3	1	2	4	2
Self-harm & violence	10	17	11	4	9	5	9	9	9	10	10	9	13	5	6	13	11	17	12	6	16
Other non-communicable	11	12	9	13	12	13	10	10	10	8	11	11	11	9	10	8	14	10	10	14	10
Maternal & neonatal	12	9	7	12	13	14	18	14	17	12	13	16	10	12	12	10	8	3	6	11	4
Substance use	13	20	18	11	10	9	16	12	11	14	8	12	17	13	14	17	18	18	18	17	18
HIV/AIDS & STIs	14	15	16	15	18	12	19	19	18	13	17	13	12	15	13	20	16	5	1	1	6
Other infectious	15	13	14	14	15	15	13	16	16	16	16	15	15	17	19	14	13	8	8	15	12
Musculoskeletal disorders	16	19	19	18	14	16	12	13	14	19	15	17	19	18	20	18	19	20	20	19	20
Enteric infections	17	7	12	16	16	18	14	17	13	18	14	14	14	16	17	12	5	4	4	9	7
Nutritional deficiencies	18	16	17	17	19	19	17	18	19	17	19	19	16	14	16	15	17	14	17	16	17
Skin diseases	19	18	15	19	17	17	15	15	15	15	18	18	18	19	18	19	20	19	19	18	19
NTDs & malaria	20	14	20	20	20	20	21	20	21	20	20	20	20	20	15	16	15	7	16	20	3
Mental disorders	21	21	21	21	21	21	20	21	20	21	21	21	21	21	21	21	21	21	21	21	21

Fonte: Global Burn of Diseases



	China	Indonesia	Fiji	Kazakhstan	Poland	Ukraine	Japan	Australia	Germany	Argentina	USA	Cuba	Peru	Mexico	Brazil	Egypt	India	Angola	Kenya	S Africa	Ghana
Cardiovascular diseases	1	1	1	1	1	1	2	2	1	1	1	1	2	2	1	1	1	9	5	3	4
Neoplasms	2	2	3	2	2	2	1	1	2	2	2	2	1	4	2	5	6	12	9	4	8
Musculoskeletal disorders	3	6	8	7	4	5	3	3	3	3	3	5	5	10	3	2	10	17	15	14	17
Chronic respiratory	4	8	5	13	9	14	9	7	6	10	7	7	14	13	14	12	4	18	19	10	18
Mental disorders	5	9	10	8	7	8	6	4	5	4	4	3	6	8	5	7	8	13	10	9	13
Neurological disorders	6	11	11	9	5	6	4	5	4	8	5	4	8	7	6	11	13	15	12	13	14
Unintentional inj	7	15	9	3	3	3	5	6	7	6	10	10	9	11	13	13	7	11	11	15	11
Diabetes & CKD	8	3	2	14	8	13	8	9	8	5	8	6	10	1	8	9	12	16	14	7	12
Transport injuries	9	14	17	15	14	15	15	15	16	14	14	17	13	12	11	6	18	10	18	8	16
Other non-communicable	10	10	6	6	10	10	10	8	10	7	9	11	7	5	7	3	9	5	6	12	6
Sense organ diseases	11	13	14	16	11	11	7	11	11	15	15	8	12	14	15	15	15	21	21	16	19
Digestive diseases	12	7	13	4	6	4	12	14	9	12	11	9	11	6	10	4	14	14	8	17	15
Maternal & neonatal	13	5	4	10	15	16	16	16	17	11	16	16	4	9	9	10	2	1	2	6	1
Substance use	14	22	20	12	13	9	17	10	13	17	6	15	19	16	16	16	21	22	22	21	22
Respiratory infections & TB	15	4	7	11	16	12	11	17	15	9	17	12	3	15	12	8	3	2	3	2	3
Skin diseases	16	17	18	18	17	18	14	13	12	16	13	14	15	17	17	17	19	20	20	18	20
Self-harm & violence	17	21	12	5	12	7	13	12	14	13	12	13	18	3	4	19	16	19	16	5	21
HIV/AIDS & STIs	18	20	22	21	21	17	21	21	21	18	18	19	16	19	19	22	22	4	1	1	5
Nutritional deficiencies	19	18	15	17	18	20	18	19	19	19	20	18	17	18	18	18	11	7	13	20	9
NTDs & malaria	20	19	21	22	22	22	22	22	22	22	22	22	22	21	20	21	20	6	17	22	2
Other infectious	21	16	19	19	20	19	19	18	20	21	21	21	21	22	22	20	17	8	7	19	10
Enteric infections	22	12	16	20	19	21	20	20	18	20	19	20	20	20	21	14	5	3	4	11	7

Fonte: Global Burn of Diseases

Early diagnosis, particularly imaging methods has been considerer an important tool to reduce mortality. (9)

2.2 IMAGING METHODS TO METASTASIS DIAGNOSIS

The routine tests to detect metastasis include X-ray, computed tomography, scintigraphy and MRI depending of phase of disease and body area that will be evaluated. This review will focus on the use of MRI for detection of metastases.

Magnetic resonance imaging (MRI) is a non-invasive technique, can provide a high spatial imaging resolution and is radiation free. MRI is one of the most powerful diagnostic imaging tools available in diagnostic imaging and it has been widely utilised in clinical practice and preclinical research studies. MRI provides a excellent imaging analysis of the bone marrow and its components with a high spatial resolution.(10) The introduction of a rolling platform mounted on top of a standard MRI examination table facilitated whole-body MRI imaging and, with the employment of fast gradient echo, T1-weighted and STIR-imaging techniques. Whole-body MRI represents a new substitute to the stepwise multimodality model for the detection of metastatic disease, multiple myeloma and lymphoma of the bone with high diagnostic precision.(10)

Whole-body magnetic resonance (MRI) imaging has been considered in many oncologic and rheumatologic indications.(11, 12) Feasibility of whole-body MR imaging has already been demonstrated for a range of diseases, including also lymphoma.(13). In oncology, the practicality and diagnostic performance of diffusion-weighted imaging (DWI) implemented to the whole body widely contributes to the effectiveness of whole-body MR imaging. The concurrent assessment of both anatomic and functional data from the DWI “hybrid” capability to whole-body MR imaging studies, allowing a sensitive and specific diagnosis of bone involvement by metastasis, multiple myeloma, and lymphoma, and evaluation of treatment response, represent as a potential biomarker.(11, 12) In arthritis of the axial skeleton, particularly spondyloarthropathies, whole-body MR imaging discloses additional lesions compared to limited axial (lumbar and pelvic) studies, mostly in the thoracic spine and thoracic wall, pelvic and shoulder girdles, and peripheral entheses and joints. Whole-body MR imaging has proven a huge potential for the study of oncologic and rheumatologic conditions, with major advantages compared to preceding imaging modalities.(11, 12) These assets include lack of ionizing radiation, one-step staging, early diagnosis, superior diagnostic

performance, ability to assess therapeutic response, and comfort for the patient **as** the technique is provides a global skeletal and multiorgan disease work-up in **a single examination.** It was also great potential for the assessment of reaction to modern treatments. **Assessment** of the whole skeleton in oncology have showed **it´s** contribution to better prognostics and treatment. The oncologic screening now also extends outside the visceral and nodal involvement. **The integration of whole-body MR imaging within the diagnostic strategy in oncology practice is** currently under **analysis**, as well as the indications for whole-body MR imaging, PET, and more restricted MRI imaging approaches. Whole-body MR imaging remains the center of current research and continuous advances, generating ample enthusiasm in multiple teams around the globe, leading to improvements in the technique and highlighting new indications. Further studies should assess the prognostic value of the initial observations and of treatment-induced modifications on whole-body MR imaging studies, in terms of complications, treatment response, and survival.(11, 12)

The major claim for whole-body MRI has been to manage considerable differences in coil requirements, slice positioning and orientation into one complete scan. Moving the patient as well as the coils are time consuming. Therefore, attempts for whole-body MRI were always associated with jeopardising spatial resolution and quality.(10)

2.3 METASTASIS OF MALIGNANT TUMORS IN PEDIATRIC PATIENTS

In the interpretation of malignant diseases, the precise measurement of tumor burden at diagnosis is a vital element in designing treatment and anticipating outcome. The occurrence of isolated metastasis of malignant tumors in pediatric patients alternates according to disease type, from 10%–12% for sarcomas to 70% for neuroblastomas with adverse prognostic factors.(14) Computed tomography (CT), magnetic resonance (MR) imaging, various scintigraphic methods and, more lately, positron emission tomography (PET) with fluorine 18 fluorodeoxyglucose (FDG) are important techniques for the staging and management of pediatric solid tumors. As survival rates for childhood malignant tumors keep on improving, with 80% of patients

estimated to achieve adulthood, the long-term sequelae of ionizing radiation are progressively more important. Thus, optional imaging methods that do not use ionizing radiation but favour similar diagnostic correctness would be predominantly beckoning. Because of its intrinsically high contrast resolution, MRI imaging is the most important alternative imaging method.(14) Results of several studies in children with a diversity of tumors demonstrated that whole-body MRI imaging was superior to others technics for allowing detection of skeletal metastasis.(5, 15, 16)

Taking into consideration the evaluation of skeletal metastases, whole-body MR imaging allowed detection of more skeletal metastases than did conventional imaging. These results are in conformity with previous studies that have shown that whole-body MR imaging with STIR was superior to bone scintigraphy for detection of skeletal metastases.(5, 15)

3 OBJECTIVE

3.1 MAIN OBJECTIVE

To evaluate the diagnostic accuracy of WB-MRI in metastasis diagnosis of children and adolescent.

4 METHODS

4.1 PROTOCOL AND REGISTRATION

This systematic review and meta-analysis was registered in international database of prospectively registered systematic reviews – PROSPERO (number CRD42018114271) and it was carried out using a protocol constructed according to Cochrane Collaboration recommendations. (17)

4.2 ELIGIBILITY CRITERIA

Studies that evaluated the WB-MRI and PET-computed tomography to assess metastatic lesion of pediatric patients (0 to 21 years) were included.

We did not restrict studies by linguistic or date criteria.

Duplicate studies and editorial were not considered. In case of duplicated studies, the one with the largest sample size was considered. In instances where essential information is not available, we excluded articles from the review. Animal, review studies were not included.

4.3 STUDY SELECTION

The following electronic databases were searched: MEDLINE (via PUBMED), EMBASE, Cochrane The Cochrane Controlled Trials Register (CCTR) Scientific Electronic Library Online (SciELO), Latin American Caribbean Health Sciences Literature (LILACS via BIREME), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science (Thomson Reuters), and www.clinicaltrials.gov.

We performed the MEDLINE search strategy and we adopted this for the other databases. Additional references were searched by crosschecking of retrieved full-text papers. We also searched the grey literature write to leading experts in the field, and search reference lists of other recent systematic reviews.

4.4 DATA COLLECTION PROCESS

Two authors (SGV and DGA) worked independently and will check the abstract and the title of query results. All potentially relevant articles will be investigated as full text. In case of disagreement, a third investigator reach an agreement.

Extraction of data was conducted by two independent authors (SGV and DGA), using a standardized instrument. The following data was extracted from the studies: First author, year of publication, study design, sample size, eligibility criteria for inclusion in the study, study population (age, sex), data on mortality and adverse events, characteristics of imaging test (F-fluorodeoxyglucose dose and time between administration of F-fluorodeoxyglucose and performance of the scan), MRI caracteristics, patient preparation and test interpretation; interval between index and PET (more or less than 3 months); assessors (number, expertise, experience, consensus procedures and learning effect data); and the numbers of patients whose results were confirmed by each type of reference standard.

4.5 RISK OF BIAS (QUALITY) ASSESSMENT

Two review authors (SGV and DGA) independently screened the risk of bias. Disagreement arose from different findings by consensus. Where additional information has required the review, authors will reassess the study when that information becomes available from the article authors. QUADAS checklist will be utilized to acess the methodological quality of the included studies. We examine the existence of publication bias graphically using a funnel plot if more than five studies are available.

4.6 STRATEGY FOR DATA COMPILATION

4.6.1 STATISTICAL ANALYSIS

We performed the meta-analyses according to the recommendations of Cochrane handbook. We used the software package Review Manager 5.3 and R to conduct meta-analyses if there were two or more eligible trials. For each study, 2x2 contingency tables consisting of true-positives, false-positives, false-negatives and true-negatives for metastasis were extracted or reconstructed. Sensitivity, specificity, positive predictive value (PPVs), negative predictive value (NPVs), and diagnostic odds ratio with relevant 95% confidence intervals (CIs) were recalculated. Diagnostic criteria were also be extracted. We performed a sensitivity analysis to assess the robustness of our analyses by excluding studies from the overall analysis of high risk of bias.

We assessed the heterogeneity of the articles by visually inspecting the forest plots and by performing the tests (P-value <0.1 representing heterogeneity). We also used the I^2 statistic to quantify inconsistencies throughout the trials. If the I^2 exceeds 50% and visual inspection of forest plots supports these findings, this is indicative of substantial heterogeneity.

5 FINAL CONSIDERATIONS

This meta-analysis showed WB-MRI had a good accuracy for the diagnosis of metastasis in children and adolescents. Whole-body MRI could potentially provide a safer non-ionizing alternative method for staging disease.

Although PET/CT is increasingly being used as the modality of choice for staging neoplasms**,** it is at the expense of an important ionizing radiation dose. Exposure to even small doses of ionizing radiation may increase the risk of secondary malignancies, particularly in children. The contribution of the radiation exposure related to imaging with long-term outcomes must also be considered. Any staging and response assessment should be conducted with a clear judgement of the risks of radiation exposure relative to the intended benefits.

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APPENDIX 1 -ORIGINAL ARTICLE

Review Article

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Whole-body magnetic resonance imaging for the diagnosis of metastasis in children and adolescents: a systematic review and meta-analysis

A ressonância magnética de corpo inteiro no diagnóstico de metástases em crianças e adolescentes: uma revisão sistemática e meta-análise

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Abstract Whole-body magnetic resonance imaging (WB-MRI) is a noninvasive imaging method that can be used to diagnose and stage tumors, as well as to assess therapeutic responses in oncology. The objective of this meta-analysis was to evaluate the accuracy of WB-MRI for the diagnosis of metastases in pediatric patients. The following electronic databases were searched: Medline, Embase, Cochrane Central Register of Controlled Trials, Scientific Electronic Library Online, Latin-American and Caribbean Health Sciences Literature, Cumulative Index to Nursing and Allied Health Literature, Web of Science, and ClinicalTrials.gov. All of the selected studies included children and adolescents with histopathological confirmation of a primary tumor. Collectively, the studies included 118 patients ranging in age from 7 months to 19 years. The pooled sensitivity and specificity of WB-MRI were, respectively, 0.964 (95% CI: 0.944–0.978; I^2 = 0%) and 0.902 (95% CI: 0.882–0.919; I^2 = 98.4%), with an area under the curve (AUC) of 0.991. We found that WB-MRI had good accuracy for the diagnosis of metastases in pediatric patients and could therefore provide an alternative to complete the staging of tumors in such patients, being a safer option because it does not involve the use of ionizing radiation.

Keywords: Whole body imaging/methods; Magnetic resonance imaging/methods; Neoplasms/diagnostic imaging; Meta-analysis; Pediatrics.

Resumo A ressonância magnética de corpo inteiro (WB-MRI) é um método de imagem não invasivo que pode ser usado para diagnosticar, estadiar e avaliar a resposta terapêutica em oncologia. O objetivo desta meta-análise foi avaliar a precisão do diagnóstico de WB-MRI no diagnóstico de metástases em crianças. Foram pesquisadas as seguintes bastes de dados: Medline, Embase, Cochrane Central Register of Controlled Trials, Scientific Electronic Library Online, Latin-American and Caribbean Health Sciences Literature, Cumulative Index to Nursing and Allied Health Literature, Web of Science, and ClinicalTrials.gov. Todos os estudos incluíram crianças e adolescentes com prova histopatológica de um tumor original. Os estudos selecionados incluíram 118 pacientes com idade variando de 7 meses a 19 anos. A sensibilidade e especificidade combinadas de WB-MRI foram, respectivamente, 0,964 (IC 95%: 0,944–0,978; I^2 = 0%) e 0,902 (IC 95%: 0,882–0,919; I^2 = 98,4%), com AUC de 0,991. A WB-MRI tem uma boa precisão para o diagnóstico de metástases em pediatria e pode potencialmente fornecer um método alternativo não ionizante mais seguro para completar o estadiamento da doença maligna em crianças.

Unitermos: Imagem corporal total/métodos; Ressonância magnética/métodos; Neoplasias/diagnóstico por imagem; Metanálise; Pediatria.

INTRODUCTION

Cancer has long been considered a major risk factor for death in the pediatric population[1]. However, when cancer is diagnosed at an early stage, the chances of cure can be high[1,2]. Various imaging methods have been used in order to assess the extent of local and distant disease[3]. Ideally, imaging examinations should be rapid, should provide high quality diagnostic information, and should be safe[2,4,5].

Imaging methods that use ionizing radiation, such as X-ray, computed tomography (CT), bone scintigraphy, and positron emission tomography/CT (PET/CT) are still routinely employed[2,4,5]. However, exposure to ionizing radiation is a major consideration in pediatric patients with

cancer. Recent improvements in magnetic resonance imaging (MRI) hardware and software have dramatically reduced scanning times, thus making MRI more appropriate for use in children[2,4,6].

Whole-body MRI (WB-MRI) is a noninvasive imaging method that can be used to diagnose and stage tumors, as well as to assess therapeutic responses in oncology[7,8]. In addition to providing coverage of the entire body, WB-MRI produces images with excellent soft tissue contrast and spatial resolution. More importantly, it does not expose patients to radiation, which makes it the ideal method for assessing the primary lesion and systemic spread in pediatric patients. The effectiveness of WB-MRI has been tested in staging patients with known malignancies, as well as in screening patients with genetic predisposition for malignancy[7,8]. One recent systematic review assessed the sensitivity of WB-MRI for the detection solely of skeletal metastases in children with primary solid tumors and found promising results[9].

The superior soft tissue contrast and more detailed depiction of bony structures are recognized as advantages of WB-MRI over PET/CT[2,10,11]. Although the use of WB-MRI in adults as an alternative to PET/CT is well established, its use for the assessment of metastases is not routine, especially in children and adolescents[2].

The objective of this systematic review and meta-analysis was to evaluate the diagnostic accuracy of WB-MRI for metastatic disease in children and adolescents.

MATERIALS AND METHODS

Protocol and registration

This systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42018114271). The protocol was developed in accordance with the Cochrane Collaboration recommendations[12].

Eligibility criteria

We included studies that evaluated metastatic lesions in pediatric patients using WB-MRI and PET/CT. Editorials and review articles were excluded, as were animal studies and studies that did not include an index test. We imposed no restrictions regarding the language or date of publication.

Study selection

The following electronic databases were searched: Medline (via PubMed), Embase, Cochrane Central Register of Controlled Trials, Scientific Electronic Library Online, Latin American and Caribbean Health Sciences Literature (via the Brazilian Regional Library of Medicine), Cumulative Index to Nursing and Allied Health Literature, Web of Science, and Clinical Trials.gov. The Medline search strategy was adopted for all of the databases. Additional references were identified through manual searches of the bibliographies of the full-text papers retrieved. In addition, we reviewed the gray literature to identify papers authored by leading experts in the field, as well as manually searching the reference lists of other recent systematic reviews.

Data collection

Two of the authors, working independently, reviewed the abstracts and titles of the eligible studies. The full texts of the potentially relevant articles were then evaluated. Disagreements were resolved through discussion with a third investigator.

The following data were extracted by using a standardized instrument: first author; year of publication; study design; study population (number, age, and sex of the patients); rates of mortality and adverse events; dose of fluorodeoxyglucose (FDG) employed; time from FDG administration to scanning; comparator imaging test; patient preparation; test interpretation; interval between index and comparator tests (≤ or > three months); assessors (number, expertise, experience, consensus procedures, and learning effect data); and the number of patients whose results were confirmed by each type of reference.

Risk of bias (quality) assessment

We screened the selected articles for risk of bias. Disagreements were resolved by consensus. Where additional information required review, we reassessed the study after that information had been obtained from the authors of the article in question. The was used in order to assess the methodological quality of the included studies, we employed the Quality Assessment of Diagnostic Accuracy Studies 2 tool[13].

Strategy for data synthesis

Timing and effect measures

A meta-analysis was performed according to the recommendations of the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy[12]. The software package Review Manager 5.3 and R were used to conduct meta-analysis. For each study, 2 × 2 contingency tables consisting of true-positives, false-positives, false-negatives, and true-negatives for metastasis were extracted or reconstructed. Sensitivities, specificities, positive predictive values, negative predictive values, and diagnostic odds ratios with 95% confidence intervals (CIs) were recalculated. Diagnostic criteria and cutoff values for metastasis were also extracted. A sensitivity analysis was performed to assess the robustness of analyses by excluding studies from the overall analysis of heterogeneity. The heterogeneity of the articles was further assessed by visually inspecting forest plots and by performing chi-square tests (values of $p < 0.1$ indicating heterogeneity). We used the I^2 statistic to quantify inconsistencies among the studies, an $I^2 > 50\%$ being indicative of substantial heterogeneity.

RESULTS

Figure 1 provides an overview of the literature search and study selection process. After duplicates had been removed, there were 283 eligible studies. During the evaluation of the titles and abstracts, we excluded 260 studies, for the following reasons: adult patients were included (n = 4); no index test was included (n = 206); there was no search for metastases (n = 26); the article type was a review article, letter, or editorial (n = 22); or it was an animal study (n = 2). The remaining 23 articles were then read in full. Of those, another 17 articles were excluded: for including adult patients (n = 7); for not including an index test (n = 6); for not searching for metastasis (n = 2); or for being a review article, letter, or editorial (n = 2). The six remaining articles were included in the systematic review, although two were excluded from the meta-analysis: one because the index study was PET only, rather than PET/CT; and one because the specificity and sensitivity values could not be calculated. Hence, only four articles were included in the meta-analysis.

Characteristics of the studies included in the systematic review and meta-analysis

Table 1 shows the characteristics of the six studies included in the systematic review. The studies included a collective total of 118 patients, ranging in age from seven months to 19 years. All of the studies included children and adolescents with histopathological confirmation of

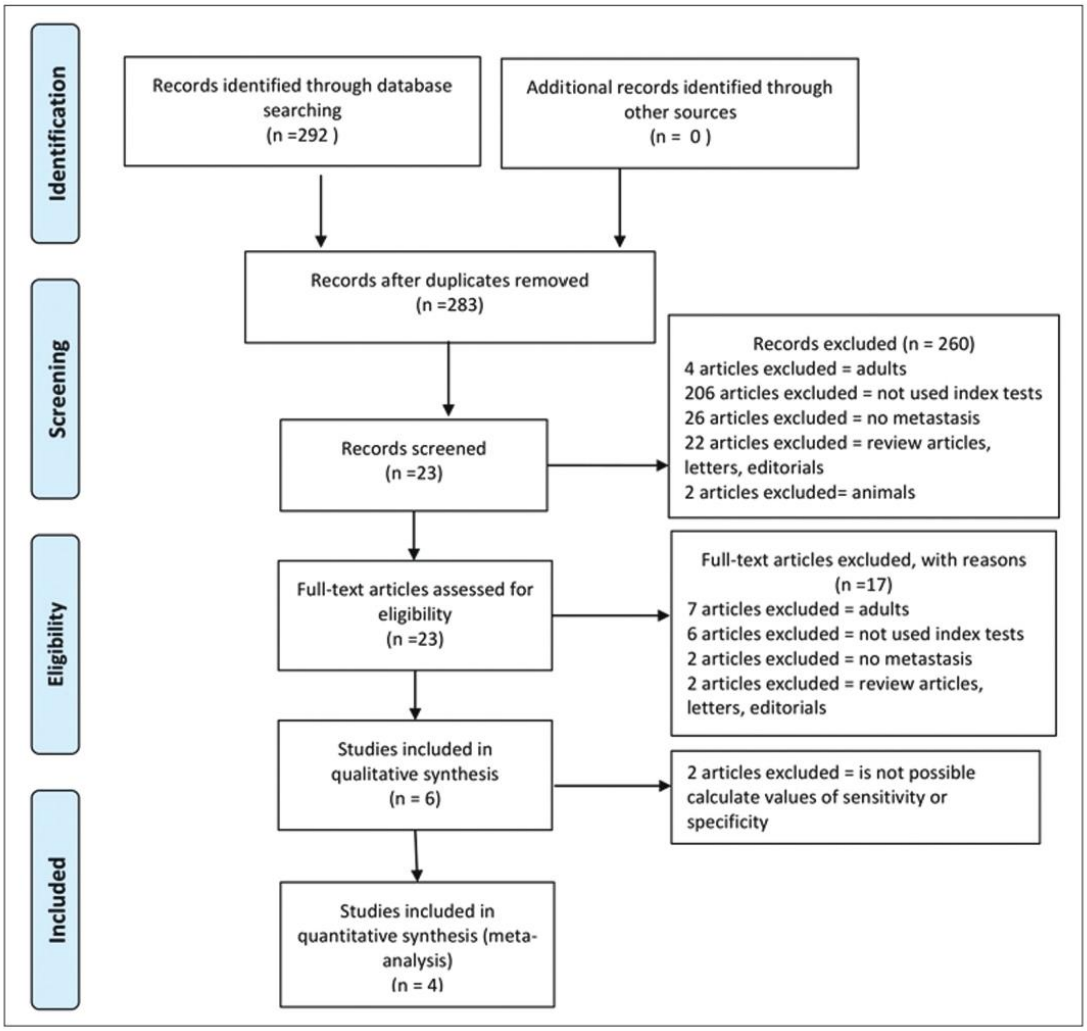

Figure 1. Flow chart of the study selection process.

Table 1–General characteristics of the selected articles

Authors	Study design	Population	Inclusion criterion	Index test	Blind	WB-MRI parameters	PET/CT parameters	Confirmed (n)
Kumar et al.[14]	Cross-sectional	N = 26; 62% males; age range, 0.58–18 years	Small-cell neoplasm	Yes	Yes	1.5 T, STIR, T1W	5,254 MBq/kg, 45 min*	26
Punwani et al.[15]	Cross-sectional	N = 29; 62% males; age range, 5–20 years	Lymphoma (26 Hodgkin and 3 non-Hodgkin)	Yes	Yes	1.5 T, STIR, RARE	5,254 MBq/kg, 60 min*	29
Ishiguchi et al.[16]	Cross-sectional	N = 13; 54% males; mean age, 2.9 ± 2.0 years	Neuroblastoma	Yes	Yes	1.5 T, STIR, DWIBS	3.7 MBq/kg, 50 min*	13
Daldrup-Link et al.[8]	Cross-sectional	N = 39; 69% males; age range, 2–19 years	Primary tumor with potential to metastasize to bone	Yes	Yes	1.5 T, STIR, T1W	3.7 MBq/kg, 60 min*	39
Littooij et al.[17]	Cross-sectional	N = 33; 61% males; age range, 6–21 years	Lymphoma	Yes	Yes	1.5 T, STIR, T1W, DWIBS	5.18–7.4 MBq/kg, 60 min*	33
Latifoltojar et al.[18]	Cross-sectional	N = 50; 64% males; age range, 5–20 years	Hodgkin lymphoma	Yes	Yes	1.5 T, STIR, T1W FLASH, DWIBS	3.7 MBq/kg, 60 min*	50

T1W, T1-weighted; RARE, rapid acquisition with relaxation enhancement; FLASH, fast low-angle shot. * Administration time.

the primary tumor. The mean sample size was 23 (range, 13–31). Of the 118 patients, 45 (66%) were male. Patients in whom there was incongruence between the findings of the two imaging modalities were further evaluated on the basis of the clinical outcomes[14], focal imaging findings[14,16], findings on follow-up evaluation, and expert panel review[15].

Five of the articles evaluated some form of WB-MRI in comparison with FDG-PET/CT[8]. Whole body diffusion-weighted imaging with background body signal suppression (DWIBS) was employed in three studies[16–18], fast spin-echo short-tau inversion-recovery (STIR) sequences were used in two studies[14,16] and T1-weighted spin-echo sequences were used in one study[8]. The maximum interval between the two examinations was 20 days. Metastases to bone and lymph nodes were found[14–16]. Three studies also investigated the diagnostic performance of the examinations for extranodal disease[15,17,18]. All WB-MRI studies were interpreted by two radiologists, whereas all PET/CT studies were interpreted by two nuclear medicine specialists.

Findings

The summary estimates obtained from the analysis of WB-MRI were a sensitivity of 0.964 (95% CI: 0.944–0.978; I^2 = 0%) and a specificity of 0.902 (95% CI: 0.882–0.919; I^2 = 98.4%). Although the heterogeneity of the sensitivity values was low (I^2 = 0%), that of the specificity values was high (I^2 = 98.4%), with an area under the curve of 0.991 (Figure 2). The study conducted by Ishiguchi et al.[16] was excluded from the heterogeneity analysis because it was found to have a high risk of bias. Thereafter, the heterogeneity of both measures decreased to 0%. In that scenario, WB-MRI identified metastasis at 778 sites in 55 patients.

The summary estimates obtained from the analysis of FDG-PET/CT were a sensitivity of 0.916 (95% CI: 0.876–0.947) and specificity of 0.958 (95% CI: 0.942–0.971). The heterogeneity of the sensitivity and specificity values

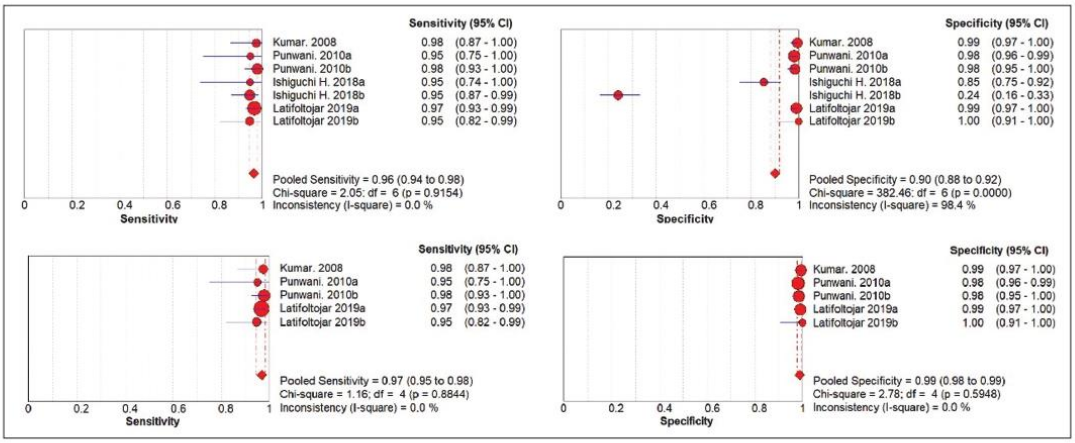

Figure 2. Forest plots of the sensitivity and specificity of WB-MRI.

was high (I^2 = 85.3% and I^2 = 95.4%, respectively). In the sensitivity analysis, performed in order to assess the robustness of our data, excluding studies from the overall analysis of the risk of bias did not decrease the heterogeneity of the sensitivity and specificity values.

Methodological quality assessment

For all of the studies evaluated, the risk of bias was classified as low, because they met the criteria for one or more of the 14 high risk of bias domains. The individual assessments for each study are shown in Table 2.

DISCUSSION

In this meta-analysis, we showed that WB-MRI has good accuracy for the identification of metastases in children and adolescents. This imaging modality could represent a safer option for tumor staging in pediatric patients, because it does not involve the use of ionizing radiation.

Although PET/CT is increasingly being used as the modality of choice for staging neoplasms[19–25], exposure to even small doses of ionizing radiation may increase the risk of later radiation-induced malignancies, particularly in children[26,27]. Any PET/CT examination for staging or for the assessment of treatment response should be conducted after a clear evaluation of the risks of radiation exposure relative to the intended benefits. Considerable progress has been made in reducing the radiation dose in pediatric CT. Despite this progress and careful management, radiation exposure is still a cause for concern in pediatric patients. However, there is now evidence that the radiation dose received by children undergoing CT at adult scanning facilities can be up to twice as high as that administered at academic pediatric centers, where it is adjusted for patient size[28].

The study that was excluded in the final analysis because of the high heterogeneity evaluated metastases to bone and lymph nodes[16]. The authors of that study reported that WB-MRI had low specificity for the detection of bone metastases. One possible explanation for this finding is the characteristic hyperintense signal of the bone marrow in the spine and pelvic bones of children and adolescents, because of the highly cellular hematopoietic bone marrow in children[29]. Ishigushi et al.[16] obtained a number of false-positives results similar to that obtained in healthy children by Müller et al.[29]. However, highly cellular hematopoietic bone marrow can be correctly identified when the hyperintense signals are similar to those of the normal hematopoietic bone marrow, which is important to bear in mind when interpreting the WB-MRI findings in pediatric patients[8,30]. In addition, although hematopoietic bone marrow shows minimal hyperintensity in comparison with skeletal muscle, tumor infiltration produces a markedly hyperintense signal much greater than that of muscle.

Of the three MRI studies that used diffusion-weighted imaging protocols[16–18], two of them[17,18] also measured the apparent diffusion coefficient (ADC). One possible advantage of applying quantitative ADC cutoffs is that it can eliminate subjectivity and improve specificity in comparison with a purely visual assessment[28]. However, it

Table 2–Test interpretation of the selected articles

Authors	Test interpretation
Kumar et al.[14]	For each patient, metastases were recorded according to body region. The body was divided into eight regions for the purpose of localization of metastases. On turbo STIR images, skeletal metastases were defined as focal or diffuse hyperintensity of marrow, greater than or equal to the signal intensity of cerebrospinal fluid. On T1-weighted images, marrow metastases were defined as areas of hypointensity, less than or equal to the signal intensity of skeletal muscle. With systemic sclerosis or on FDG-PET, metastatic disease was defined as a focal area of increased radionuclide uptake relative to adjacent and/or contralateral normal tissue.
Punwani et al.[15]	MRI: The body was divided into 11 nodal areas by standard anatomic definitions. Disease positivity was defined as a mass with a short-axis dimension greater than 1 cm. PET/TC: Disease positivity was defined as the presence of lymph nodes with focal FDG uptake greater than that of the background.
Ishiguchi et al.[16]	The presence of lymph node metastasis was assessed in eight regions. Bone metastasis was investigated in 17 bone segments. On whole-body DWIBS, the signal intensity of skeletal muscles was used as the reference standard for the judgment of positive results. On ^{18}F-FDG PET/CT, ^{123}I-metaiodobenzylguanidine scintigraphy/single-photon-emission CT/CT, and bone scintigraphy/single-photon-emission CT, the loci where uptake was visibly higher than the activity of adjacent areas were considered uptake-positive. On CT, characteristic massive lesions corresponding to the sites of lymph nodes were defined as metastasis-positive findings, as were focal or diffuse skeletal lesions with or without deformity of cortical bone.
Daldrup-Link et al.[8]	For all imaging modalities, lesion number and location were determined. On T1-weighted spin-echo images, a metastatic bone or bone marrow lesion was defined as focal or diffuse hypointense bone marrow signal intensity relative to adjacent normal bone marrow. In patients over 10 years of age, neoplastic marrow was defined as that with a signal that was hypointense or isointense in relation to the adjacent muscle tissue. FDG-PET: a metastatic bone lesion was defined as a focal area of increased radionuclide uptake relative to the adjacent and contralateral normal tissue.
Littooij et al.[17]	Nodal regions included cervical (including supraclavicular nodal site), axillary, infraclavicular, mediastinal, hilar, para-aortic, mesenteric, pelvic and inguinal lymph node regions. Lymph nodes were considered positive for lymphomatous involvement if their short-axis diameter exceeded 10 mm on coronal T1- and T2-weighted STIR images. Extranodal sites included the thymus, pleura, lung, spleen, liver, kidney, bowel, bone marrow, and soft tissues. Diffusion-weighted imaging was used in order to detect potentially involved nodal and extranodal sites.
Latifoltojar et al.[18]	MRI: The disease status for the same 18 nodal disease sites and 14 extranodal disease sites. The ADC was measured by placing a region of interest in the largest cross-section of the node on the ADC map, guided by anatomically matched axial fat-suppressed T2-weighted MRI. PET/TC: Definitions of nodal disease based on long-axis size and FDG uptake in comparison with background activity.

is clear that there is an overlap in ADC values between malignant lymph nodes and normal/reactive lymph nodes, so the optimal ADC cutoff remains unclear and requires further investigation[18].

We observed that the studies that utilized only STIR sequences for detecting bone metastasis[15,28] achieved the best specificity and sensitivity, with no heterogeneity, and that the method had a diagnostic performance similar to that of PET/CT. Coronal STIR sequences are sensitive to soft-tissue and bone abnormalities because of their additive proton density-weighted, T1-weighted, and T2-weighted contrast with inherent fat suppression. Most pathological tissues are proton-rich and have prolonged T1 relaxation and T2 decay times, resulting in high signal intensity on fast STIR images[28]. Kumar et al.[14] used coronal STIR parallel acquisition. Studies have also suggested that STIR WB-MRI allows excellent delineation of focal lesions that show inadequate FDG uptake, due to its high tissue contrast[31]. Punwani et al.[15] used respiratory- and cardiac-gated axial and coronal STIR half-Fourier rapid acquisition with relaxation enhancement.

Although PET/CT had high sensitivity and specificity, the data were quite heterogeneous. One possible explanation is differences in the timing of the follow-up imaging and in the baseline neoplasms evaluated. The specificity of FDG-PET/CT was lower for the detection of bone metastases than for the detection of lymph node metastases. However, the efficiency of FDG-PET/CT for distinguishing bone metastasis from neuroblastoma was comparable to what has been reported previously[17,32]. In 54% of the subjects evaluated by Ishiguchi et al.[16], nuclear medicine scans were taken at least 13 days after the start of treatment, including chemotherapy. The high (26.9%) false-positive rate in that study could therefore be explained by the well-known high uptake of FDG in bone marrow under chemotherapy[33].

The limitations of this meta-analysis and systematic review are related to the small sample sizes in the available studies. However, the number of sites investigated was considered sufficient to support the conclusions. In addition, only one of the studies evaluated the use of WB-MRI for the detection of post-treatment disease.

In conclusion, this systematic review and meta-analysis showed that WB-MRI has good accuracy for the diagnosis of metastatic disease in children and adolescents. Because it does not expose patients to ionizing radiation, WB-MRI could represent a safer alternative for cancer staging.

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