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An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: Systematic review.

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Abstract

Purpose/Objective: Rhabdomyosarcoma (RMS) management depends on risk stratification at diagnosis and treatment response. Assessment methods include CT, MRI, bone scintigraphy, histological analysis and bone marrow biopsy. Advanced functional imaging (FI) has potential to improve staging accuracy and management strategies.

Materials and Methods: We conducted a systematic review (PROSPERO 2013:CRD42013006128) of diagnostic accuracy and clinical effectiveness of FI in histologically proven paediatric RMS. PRISMA guidance was followed. We searched 10 databases to November 2013. Studies with ≥10 RMS patients which compared PET, PET-CT or DWI MRI to conventional imaging at any treatment stage were included. Study quality was assessed. Limited, heterogeneous effectiveness data required narrative synthesis, illustrated by plotting sensitivity and specificity in ROC space.

Results: Eight studies (six PET-CT, two PET) with 272 RMS patients in total were included. No DWI-MRI studies met inclusion criteria. Pooled estimates were not calculated due to sparseness of data. Limited evidence indicated initial PET-CT results were predictive of survival. PET-CT changed management of 7/40 patients. Nodal involvement PET-CT: sensitivity ranged from 80% to 100%; specificity from 89% to 100%. Distant metastatic involvement: PET-CT sensitivity ranged from 95% to 100%; specificity from 80% to100%. Data on metastases in different sites were sparse. Limited data were found on outcome prediction by PET-CT response.

Conclusions: PET/PET-CT may increase initial staging accuracy in paediatric RMS, specifically in the detection of nodal involvement and distant metastatic spread. There is a need to further assess PET-CT for this population, ideally in a representative, unbiased and transparently selected cohort of patients.

Article Summary: Strengths and limitations of this study

- This is the first systematic review of the use of advanced functional imaging in the management of rhabdomyosarcoma in children and young people.
- No studies of DWI-MRI in managing rhabdomyosarcoma of sufficient quality for inclusion were identified.
- Rigorous methodology identified the limitations of the existing research supporting this use of PET/PET-CT in the staging, prognosis development and outcome assessment of diagnosed RMS.
- Paucity of evidence prevented meta-analysis of sensitivity and specificity and contributed to considerable uncertainty around the true value of PET-CT, including whether it should be considered as an additional or a replacement diagnostic tool.
- Potential benefits of PET-CT in increasing staging accuracy were identified: specifically identification of nodal involvement and metastatic spread. Clear research recommendations for incorporation of PET-CT into future treatment trials are presented.

Background

Rhabdomyosarcoma (RMS) accounts for over 50% of sarcomas in children and young people. (1) (2) Incidence is 4.6 per million aged < 20 years. RMS frequently presents as a soft-tissue mass. The commonest sites of origin are head and neck, genitourinary tract, and limbs. Treatment is based on a multimodality approach including neoadjuvant chemotherapy, surgery where possible, radiotherapy, and adjuvant chemotherapy. Overall outcomes have improved but remain suboptimal, with three-year event-free survival (EFS) rates for patients with localised disease of around 60% in Europe and a corresponding overall survival (OS) of 80%.(3, 4) Patients who present with metastatic disease have much poorer prognoses and should be considered for novel treatment strategies. Correct staging is imperative.

Current treatment protocols rest on decisions at several points during therapy. Full initial staging employs cross-sectional imaging of the primary tumour (often with MRI); further cross-sectional imaging of the chest, abdomen, and pelvis; a radiolabelled bone scan; and pelvic bone marrow biopsies. These methods are also used to assess disease response for treatment modification and at the end of treatment as ongoing surveillance.(3) The usefulness of assessment methods is under ongoing evaluation; a recent European paediatric Soft tissue Sarcoma Group (EpSSG) analysis showed that otherwise low risk patients are unlikely to have isolated bone metastasis; in future bone scans may be omitted for these patients.(5) (K. McHugh, personal communication). Current assessment methods give discordant results at post-chemotherapy evaluation, highlighting the potential importance of functional imaging (FI).(6)

FI has been incorporated into management of other malignancies (e.g. staging non-small-cell lung cancer (NSCLC) and assessing treatment response in Hodgkin lymphoma) after extensive reviews found strong evidence for PET-CT.(7) It was found to be cost-effective for assessment of recurrent colorectal cancer,(8) but was less useful than non-nuclear technologies (e.g. functional MRI and nodal biopsies) in regional node evaluation in breast cancer.(9) Previous systematic reviews with meta-analysis of sarcomas generally have found uncertain and heterogeneous results.(10, 11)

This is the first systematic review of FI in children and young people with RMS diagnosis. FI has potential as an additional imaging technique or replacement for current imaging modalities for initial staging and/or response assessment.

Objective

To assess the role of FI (PET/PET-CT and DWI-MRI) in the management of RMS in childhood and adolescence and to consider its potential as a tool for improving both diagnostic (staging) and prognostic evaluation. Assessment of FI for treatment response and end of treatment evaluations were secondary aims. The review was not designed to assess the differential diagnosis of RMS in patients with suspected sarcoma.

Methods

We undertook a systematic review of the diagnostic accuracy and clinical effectiveness of PET, PET-CT and DWI MRI for assessment of histologically proven RMS in children and young people. The protocol was registered on PROSPERO (2013:CRD42013006128)(12) and PRISMA guidance adhered to. We consulted three public patient (PPI) representatives while writing the protocol and they contributed to the selection of outcomes assessed.

We searched 10 databases (including MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) from inception to November 2013 without restrictions on publication status, date or language (see appendix 1 for full list of databases and complete search strategies).

The following prespecified inclusion criteria were applied:

- **Participants**: Children and young people aged 0 to 24 years of age who are diagnosed with histologically proven RMS of any type. Studies with mixed tumour types will be included if outcome data for RMS patients are reported separately for at least one outcome. Studies with mixed populations of children/young people and adults were included where it was clear that a majority of patients were children/young people.
- **Interventions:** FI: PET +/- CT, or DWI-MRI used at any point in the management of RMS
- **Comparator:** Conventional imaging (One or more of contrast-enhanced CT or standard MRI, Technetium-99m bone scintigraphy)
- **Primary outcome:** EFS or OS at any time point.
- **Secondary outcomes:** Relapse rates, quality of life, adverse events or acceptability of the technology (by patient, carer or health professional), histological confirmation via lesional biopsy, or independent imaging or comparative classification of staging and risk classification of disease and treatment alteration in the light of imaging tests performed
- **Study design:** Prospective and retrospective studies of any design with at least 10 RMS patients for whom separate data is available for at least one outcome (following a protocol amendment due to lack of data; originally studies were required to include ≥ 20 RMS patients).

Studies were assessed for inclusion and appraised for quality by two independent reviewers. We used a tool adapted from previous HTA reviews(13, 14) for quality assessment of case series. We also assessed the reliability of the PET process.(15)

Data were extracted onto a prespecified form using the EPPI-Reviewer software by one researcher and checked by a second (forms were piloted by two independent researchers). A third researcher was consulted where necessary. Patient-level data were extracted to enable construction of 2x2 tables for detection of nodal involvement and distant metastases. Sensitivity and specificity of PET and conventional imaging were calculated for each study and plotted in ROC space. There were insufficient data to calculate pooled sensitivity and specificity.

At all stages of the review process we attempted to contact study authors about uncertain, missing or incomplete data.

Due to the limited and incomplete nature of the data reported, data at the level of individual primary, nodal or metastatic sites were summarised in a narrative synthesis. Data on survival, tumour response and treatment modification were very limited and heterogeneous so were also summarised narratively.

Results

Quantity and quality of evidence

We identified 1725 unique records and assessed 300 as full-text papers. Six studies of PET-CT(16-21) and two of PET(22, 23) were included; these were reported in a total of 15 publications(16-30) and

the most up-to-date data were used in the review (see Appendix for flow diagram). All studies had a full primary English publication; in one case, survival data were available only in abstract.(29)

Seven studies included only RMS patients;(16-19, 21-23) one included a minority of RMS patients with separate data.(20) Data were reported on a total of 272 RMS patients. Two additional studies reported in abstract included >10 RMS patients but were excluded as, despite author contact, we were unable to obtain separate RMS patient data.(31, 32) One study reported separate RMS data only for the subset of patients with a primary tumour in the extremities and was included because of this data.(20) Three studies included one or more adults aged ≥25 years; these studies were included because it was clear that the great majority of patients were children/young people; median ages were 11 and 13 in two studies(17, 23) and the mean age in the third was 19.8.(19)

No studies of DWI-MRI met inclusion criteria (even after protocol amendment from >20 cases to >10 cases); only studies that assessed it for differential diagnosis with very few RMS cases were found.(33-39) These studies of DWI are discussed elsewhere. [Norman et al, Paed Radiol, in press 2014] A full list of excluded studies is available on request.

All studies used fludeoxyglucose (18F) as the radiopharmaceutical for PET. Most studies reported using all possible conventional imaging techniques as a comparator to PET or PET-CT (see table 2). The reference (gold) standard (as distinct from the comparison with conventional imaging) was typically a mixture of histopathology, clinical examination and follow-up.

Included studies often involved more children with unfavourable prognoses than would be expected in clinical practice: 52% of the patients in the series had an unfavourable, alveolar histology compared to 20-30% in clinical practice.(1) Histology was generally not well described and information on genetic predispositions was limited to one study which noted that no patient had a history of familial cancer syndrome. (21) Where reported, large numbers of patients had stage III or IV disease compared to around 15% with stage IV disease in clinical practice.(40) Several studies included higher numbers of patients with primary tumours of the extremities. Study characteristics are summarised in Table 1.

[table 1 about here]

All studies were opportunistic case series. Most were retrospective and did not comprise consecutive series of patients. It was often unclear how representative of the eligible population the included patients were. Details of FI procedures were often not reported. See Appendix 2 for a summary of quality assessment results. Outcome reporting was inconsistent and often incomplete. In some cases was this remedied by contacting authors.

Survival and related outcomes

Only one study (N=41) reported data on overall survival (OS).(22) This found that metabolic activity of the primary tumour on PET-CT had prognostic significance for survival (p=0.007). Also predictive of survival were PET-CT detection of nodal involvement (P=0.016), PET-CT detection of metastases (P=0.002), and a composite outcome (PET group; P=0.002). Dichotomisation around the point $SUV_{max}/SUV_{liver} = 4.6$ was also predictive (P=0.002). Nodal and metastatic involvement retained statistical significance in a multivariate analysis; primary tumour intensity did not.

Three studies reported data on event-free survival (EFS).(17, 22, 29) One (N=41) found similar results for EFS as for OS, with prognostic significance for primary tumour intensity (P=0.005), lymph node detection (P=0.008), and metastases detection (P=0.01). Dichotomisation around the point SUV_{max}/SUV_{liver} = 4.6 did not predict EFS. Another study (N=94) reported trends towards prognostic significance for PET-CT results dichotomised by SUV_{max} = 7.0 at initial staging (P=0.08) and by pre-RT PET-CT-positivity (after median 15 weeks chemotherapy) (P=0.06).(17) At post-RT assessment PET-CT-negative patients were significantly less likely to relapse than PET-positive individuals (P=0.02). The third study (N=38), available as an abstract, reported no prognostic significance of PET-CT at any point.(29) None of these reports demonstrated an additional prognostic value of metabolic activity indices above conventional prognostic criteria.

One study reported tumour response.(16) In a subset of 13 patients PET-CT was more likely than conventional imaging to show complete response to treatment; most of these patients were assessed by conventional imaging as having a partial response and twelve were in remission at follow-up.

Treatment alteration

PET-CT changed the management or treatment course of 7/40 patients in studies that reported this outcome.(16, 20, 21)

Quality of life and acceptability

There were no data on quality of life or acceptability of the technology. All three PPI representatives considered that additional scans (and their associated requirements of time, travel, and additional procedures) were worthwhile if they could provide additional information to inform the treatment plan and/or prognosis.

Diagnostic data

Lymph nodes

For nodal involvement, PET-CT or PET showed sensitivity of 80% (1 study)(18) or 100% (3 studies)(19-21) and specificity of 89% to 100% at the patient level. This compared to sensitivity of between 67% and 86% and specificity of 90% or 100% for conventional imaging (Table 2 and Figure 2). The ROC space 'cross-hairs' plots show each study's estimates of sensitivity and specificity as a marker at the point estimate, with 95% confidence intervals demonstrated by lines. In reading such graphs, tests with better discriminatory ability fall in the top left corner of the plot, and non-discriminatory tests fall on a 45° line between the bottom left and top right.(41)

[Table 2 about here]

[Figure 1 about here]

Nodal level data from three studies also indicated that PET-CT was able to detect more positive nodes than conventional imaging with very few false positives.(16, 18, 21) One study with fully reported data found sensitivity and specificity of 100% for PET-CT compared to 75% and 94% for conventional imaging. (16) Where reported, PET-CT generated many fewer indeterminate results (1 versus 18/35) and more true negatives than conventional imaging .(18)

Distant metastases

For detection of distant metastatic sites, PET-CT had a sensitivity of 95% (1 study)(19) or 100% (2 studies)(18, 21) and specificity of 80% to 100% at the patient level. This compared to sensitivity of between 17% and 83% and specificity of between 43% and 100% for conventional imaging (Table 2 and Figure 2).

[Figure 2 about here]

Site level data from another study also found higher sensitivity and specificity (100% and 96%) for PET-CT compared to 66% and 91% for conventional imaging.(16)

Information on detection of metastases in different sites was extremely limited and reported at the level of individual cases (Table 3).(16, 18, 19, 21) There were indications from this very limited evidence base that PET-CT may be superior to CI for detection of bone lesions, in that both additional lesions and patients with otherwise undetectable bone involvement were identified. (16, 18, 19, 21) The number of false positives was low. PET-CT may also have potential to specifically identify marrow involvement in some patients but this finding is unclear and based on tiny numbers of patients; sensitivity appeared limited. (18) PET-CT appeared poor for detection of lung metastases.(18, 21) There were indications that PET-CT may perform better than conventional imaging in detecting soft tissue lesions in non-pulmonary locations,(18, 19) possibly including distal nodal involvement. (21)

[Table 3 about here]

Primary tumours

The ability of PET-CT to detect primary tumours was good; only one known tumour site was missed(16) and one previously occult primary was identified;(21) further details are in Appendix 3.

Discussion

We identified eight studies (272 patients) of PET or PET-CT in children and young people with RMS and no eligible studies of DWI-MRI.

The studies identified had multiple limitations. All studies were opportunistic case series open to a range of biases. As such they addressed multiple aspects of the use of PET in RMS management. Patients already had a diagnosis of RMS so the studies were not diagnostic in the conventional sense; rather they were concerned with accuracy of staging, determination of prognosis and, in some cases, evaluation of treatment outcome. The review was not designed to assess the value of PET-CT in imaging primary tumours, as the requirement for histologically proven RMS diagnosis meant that almost all patients had a known tumour site. This makes comparison to earlier reviews that included all sarcomas unhelpful.(10)

The studies included a higher proportion of more challenging cases than expected in clinical practice. Imaging methodology was not well reported. Duplicate blinded evaluation of the FI results relative to the conventional imaging results or reference standard was often absent or unclear. Results were often not clearly or fully reported and data remained inconsistent and incomplete even after

contacting authors. Our findings are therefore tentative and require confirmation by further research.

PET-CT was consistently somewhat better than conventional imaging at identifying patients with nodal involvement at initial staging and was clearly more sensitive to individual positive nodes, with fewer indeterminate results. PET-CT appeared to improve sensitivity in identification of distant metastases including identifying patients in whom distal metastatic involvement was not otherwise indicated. There is a suggestion of a role for PET-CT in detection of bone involvement but a great deal of uncertainty. Data for lung lesions are sparse and do not suggest utility. These results accord with reviews of PET-CT in staging of osteosarcoma(42) and PET in general diagnosis of pulmonary nodules.(43)

There is very limited evidence on use of PET-CT for treatment response and end of treatment evaluation. Only three studies investigated the primary outcome of survival and one evaluated tumour response. PET-CT at initial staging may have predictive value for OS and EFS. The role of PET-CT in the assessment of treatment response before and after radiotherapy is unclear. PET-CT may be superior at ascertaining complete response to chemotherapy but this is based on one small study. The tentative findings of this review suggest that the performance of PET-CT in RMS may be closer to that in Hodgkin lymphoma, NSCLC(7) and colorectal cancer(8) than in breast cancer.(9)

None of the studies reported data on the impact of FI or conventional imaging on quality of life or acceptability to any identified stakeholder group. Our PPI representatives indicated that potential additional information was highly valued and mattered more than a need for additional procedures and the resource implications of additional scans. They were particularly supportive of FI in further research with potential to clarify possible benefits of additional or alternative imaging procedures.

This systematic review represents the first thorough evaluation of the international evidence on FI in the management of childhood and adolescent RMS. Extensive searching without language restrictions ensured the inclusion of all relevant studies. We made substantial efforts to obtain supplementary data from authors. Although some studies contained patients aged >24 years we are confident from the mean/median ages reported that these were a small minority of the populations and that the relevance of the studies to the paediatric population was not significantly impacted. Excluding these studies would have resulted in the loss of data on a significant proportion of documented PET use in paediatric RMS. Studies were quality assessed and synthesised to provide an unbiased comprehensive assessment of the evidence

The key limitation was our inability to obtain all relevant data despite contacting authors. In particular we are aware of two case series in sarcoma patients which included >10 RMS patients that we could not include as authors were unable to provide separate data on RMS cases. The lack of complete patient-level data from all included studies meant we were unable to calculate pooled estimates for the sensitivity and specificity of FI and conventional imaging. However, even had we acquired full data on all known paediatric RMS patients, the total number would have remained under 300. Any answers to the review questions would have remained tentative and uncertain. There is an urgent need for more reliable disease assessment at all stages of RMS management. PET-CT may be an option for this with sufficient prospective testing through incorporation into any future trials of RMS treatments.

Conclusion

This review highlights potential from PET-CT in imaging of children and adolescents with RMS but there is a high level of uncertainty in these data and their relevance to clinical practice. Limited evidence suggests that PET / PET-CT has potential to increase initial staging accuracy, specifically detection of nodal involvement and distant metastatic spread. There is little evidence on the impact of PET-CT in assessment of therapeutic response or post-treatment assessment. The ultimate impact of FI with PET-CT on treatment outcomes could not be addressed and it remains unclear whether and how increasing accuracy at initial staging might alter patient management and survival. It was impossible to determine whether PET-CT could replace any current imaging tests or should be used as an adjunct.

DWI-MRI has been insufficiently researched to answer questions of utility in RMS; the very limited evidence base for this is discussed elsewhere (Norman et al; Paed radiol 2014; in press).

Recommendations for further research.

- A representative, unbiased, and transparently selected cohort of patients (entering a treatment RCT) should be identified. All patients should be evaluated using PET-CT as an adjunct to conventional techniques at initial staging, treatment response, and end of treatment.
- The protocol should specify interim data analysis, potentially enabling PET-CT to replace one or more conventional staging techniques or substantially modify treatment delivery by response assessment.
- Results should be fully reported and individual patient data made available.
- Methodology of the PET-CT process should be standardised and reported fully. This should include independent reading of scans by multiple assessors blinded to conventional imaging and clinical/histological results.
- Appropriate qualitative methodologies should be used to assess the additional burden of treatment to patients and healthcare system, and resource use prospectively evaluated.
- Further comparative research on DWI-MRI in RMS is needed; researchers using this technology in RMS patients should be encouraged to publish case series in the first instance.

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Author contributions: BP Designed concept for study, wrote initial draft of protocol, supervised review, undertook analysis, reviewed and edited manuscript; GN Contributed to protocol, screened and assessed all papers, developed and conducted data extraction, wrote initial and edited later drafts of manuscript; DF: Contributed to protocol, screened and assessed all papers, developed and conducted data extraction, reviewed and edited the manuscript; KL designed and undertook the search strategy, managed the study database and reviewed and edited the manuscript; JC, MJ, SG, DL, HM, KM contributed to the protocol, provided clinical advice to the review, reviewed and edited the manuscript.

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Table 1: Participant characteristics

Study	Intervention [Conventional imaging methods] (Ref standard)	No (% male)	Age (years): Mean/ median (range)	Primary tumour location								Histology (%)	Tumour stage (%)	Risk classification (%)
				Orbit	HN (nPM)	HN (PM)	Trunk	Extremity	GU (nBP)	GU (BP)	Other			
Baum (2011)(22) Germany	PET-CT (whole body) 5 patients received PET only. [MRI, ultrasound, contrast-enhanced CT] (clinical diagnosis inc. CT)	41 (58)	9.9[a] (1 to 20)	2	5	2	0	19	2	3	8	Alveolar 24 (59) Embryonal 17 (41)	Not reported	Group 1 0 Group 2 11 (27) Group 3 18 (44) Group 4 12 (29)
Dharmarajan (2012)(17) USA	PET-CT (coverage NR) Minority had no CT available.[CT] (NR)	94 (50)	11[b] (0.2 to 43)	5	3	34	19	21	3	9	0	Alveolar 44 (47) Embryonal 49 (52) Other 1 (1)	Stage I 10 (11) Stage II 4 (4) Stage III 48 (51) Stage IV 32 (34)	Group 1: 0 Group 2: 9 (10) Group 3: 53 (56) Group 4: 32 (34)
Eugene (2012)(16) France	PET-CT (whole body) [Bone marrow biopsy, chest radiograph, CT, MRI, bone scintigraphy] (clinical exam, histopathology, follow-up, US)	23 (70)	8.7[b] (0.75 to 21.6)	5	3	4	0	1	1	4	4	Alveolar 9 (39) Embryonal 13 (61) Other 1 (0)	Not reported	Not reported
Federico (2012) (18) USA	PET-CT (Vertex to toes) [chest CT, CT/MRI of primary and local-regional nodal basin, bone scan] (Clinical assessment, histology)	30 (57)	7.3[b] (1.3 to 23.5)	0	4	8	4	9	0	3	2	Alveolar 11 (37) Embryonal 14 (47) Other 5 (16)	Not reported	Unclear
Klem (2007)(23) USA	PET (Vertex to upper thigh, lower extremities depending on tumour location and clinical suspicion) [CT, MRI or bone scan] (Imaging, pathology, clinical findings at tumour board)	24 (42)	13[b] (1.3 to 56)	0	3	11	4	4	0	2	0	Alveolar 14 (58), Embryonal 10 (42)	Stage I 2 (8) Stage II 2 (8) Stage III 18 (75) Stage IV 5 (21)	Group 1 0 Group 2 1 (4) Group 3 18 (75) Group 4 5 (21)
Ricard (2011) (21) France	PET-CT (head to upper thigh (4 patients had scans inc legs)) [MRI , CT (primary), bone	13 (92)	9.6[b] (1.8 to 19.1)	0	4	2	0	0	0	3	4	Alveolar 10 (77), Embryonal 3 (23)	Stage I 4 (31) Stage II 1 (8) Stage III 2 (15) Stage IV 6 (46)	Not reported

	scintigraphy (metastases)] (histopathology and clinical evaluation at tumour board)													
Tateishi (2009)(19) Japan	PET-CT (head to mid-thigh (2 patients had scans inc legs)) [chest radiograph, whole body CT, MRI (primary), bone scintigraphy] (Histopathology, clinical follow-up, CSF evaluation)	35 (69)	19.8[a] (3 to 38)	1	0	18	8	8	0	0	0	Alveolar 22 (63), Embryonal 12 (34) Other 1 (3)	Stage I:Initial 3 (13) Restage 7 (70) Stage II:Initial 21 (87) Restage 3 (30)	Not reported
Volker (2007)(20) Germany	PET (whole body) [radiography (primary), chest x-ray, CT, MRI (primary and additional regions where clinically indicated), US (abdominal and additional regions where clinically indicated), bone scintigraphy] (Histopathology, clinical examination including follow-up)	46 (52) *	12.9[a] (1 to 18)*	Not reported								Not reported	Not reported	Not reported

[a]Mean [b]Median *Whole group (data not available for RMS patients only) HN head and neck nPM non-parameningeal PM parameningeal GU genitourinary nBP non-bladder/prostate BP bladder/ prostate

Table 2: Summary of patient level diagnostic data: detection of nodal and distant metastatic involvement

Study	Image	N	Sensitivity		Specificity	
			PET	conventional imaging	PET	conventional imaging
Nodal involvement						
Federico (2012)(18)	PET-CT	30	0.8	-	1	-
Ricard (2011)(26)	PET-CT	13	1	0.75	0.89	1
Tateishi (2009)(19)	PET-CT	35	1	0.86	0.95	0.9
Volker (2009)(20)	PET	4*	1	0.67	1	1
Distant metastatic involvement						
Federico (2012)(18)	PET-CT	30	1	0.17	0.92	1
Ricard (2011)(26)	PET-CT	13	1	0.83	1	0.86
Tateishi (2009)(19)	PET-CT	35	0.95	0.55	0.8	0.43

*Total N=46; 12 RMS; data available on 4 with extremity primary tumour.

Table 3: summary of detection of metastatic sites

Study	Image	N	Bone	Bone marrow	Lung	Soft tissue	Distant nodes
Federico (2012)(18)	PET-CT	30	PET-CT detected 3/4 patients. CI detected 1/4	FI detected 2/4 patients. CI detected 0	PET-CT detected 4 nodules compared to 7 (in 6 patients) detected by CI.	PET-CT detected multiple metastatic sites in 2 patients missed by CI. Only one of these was detectable on physical examination	
			4 other patients had some bone abnormality on PET-CT but not CI. Two of these were confirmed positives at follow-up				
Ricard (2011)(26)	PET-CT	13	All 4 patients identified by both PET-CT and CI. PET detected 8 more lesions across 3 patients		PET-CT detected 1/2 patients compared to 2/2 patients by CI.	PET-CT and CI identified 2/2 patients; PET-CT identified 4 sites compared to 3 for CI	PET-CT detected 4/4 patients compared to 3/4 for CI. PET-CT detected an additional 5 positive nodes.
Tateishi (2009)(19)	PET-CT	35	PET-CT generated 3 false positives and 1 false negative. CI generated 3 false positives and 6 false negatives			PET-CT identified 3 patients missed by CI	
Eugene (2012)(16)	PET-CT	23	PET-CT identified 3/3 patients compared to 2/3 for CI. CI also generated 1 false positive compared to 0 for PET-CT		PET-CT and CI both generated 1 false positive	PET-CT generated 1 false positive compared to 0 for CI	

Figure Legends

Figure 1: Sensitivity and specificity of PET-CT versus conventional imaging in detection of nodal involvement plotted in ROC Space

Figure 2: Sensitivity and specificity of PET-CT versus conventional imaging in detection of distant metastatic involvement plotted in ROC Space

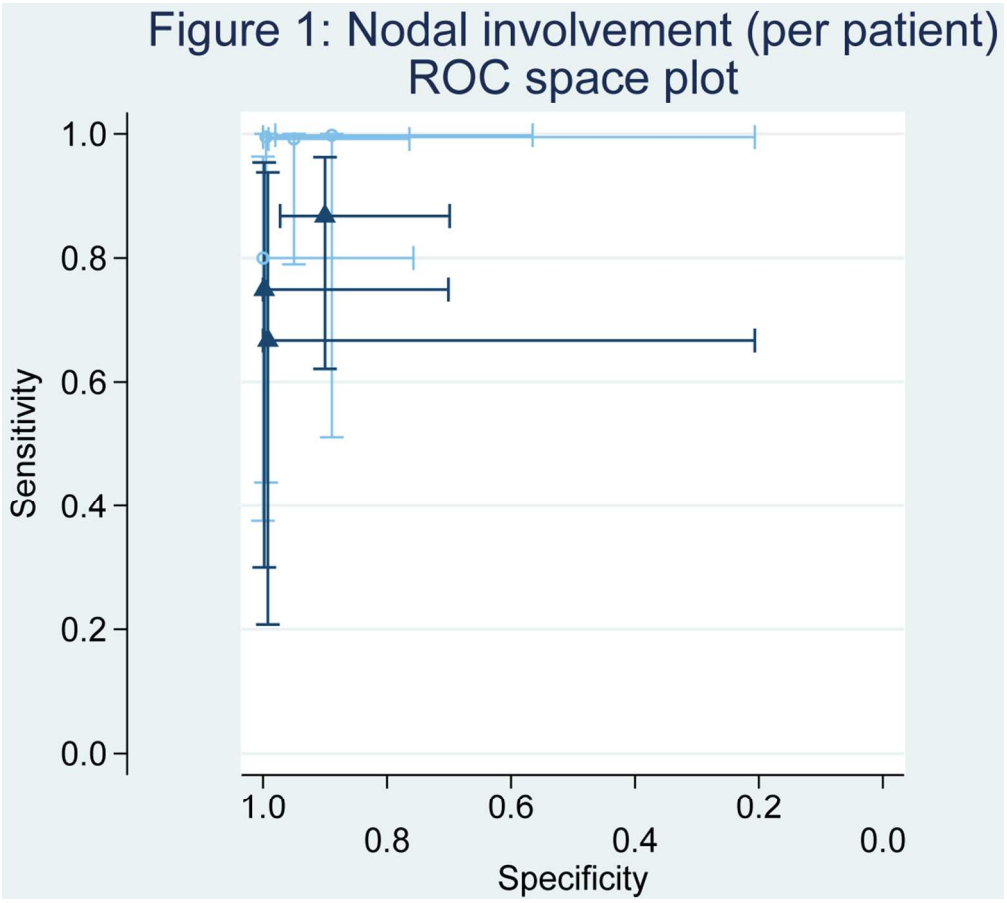

Figure 1. Nodal involvement (per patient): ROC space plot.

Light blue denotes PET-CT
Dark blue denotes conventional imaging
105x94mm (300 x 300 DPI)

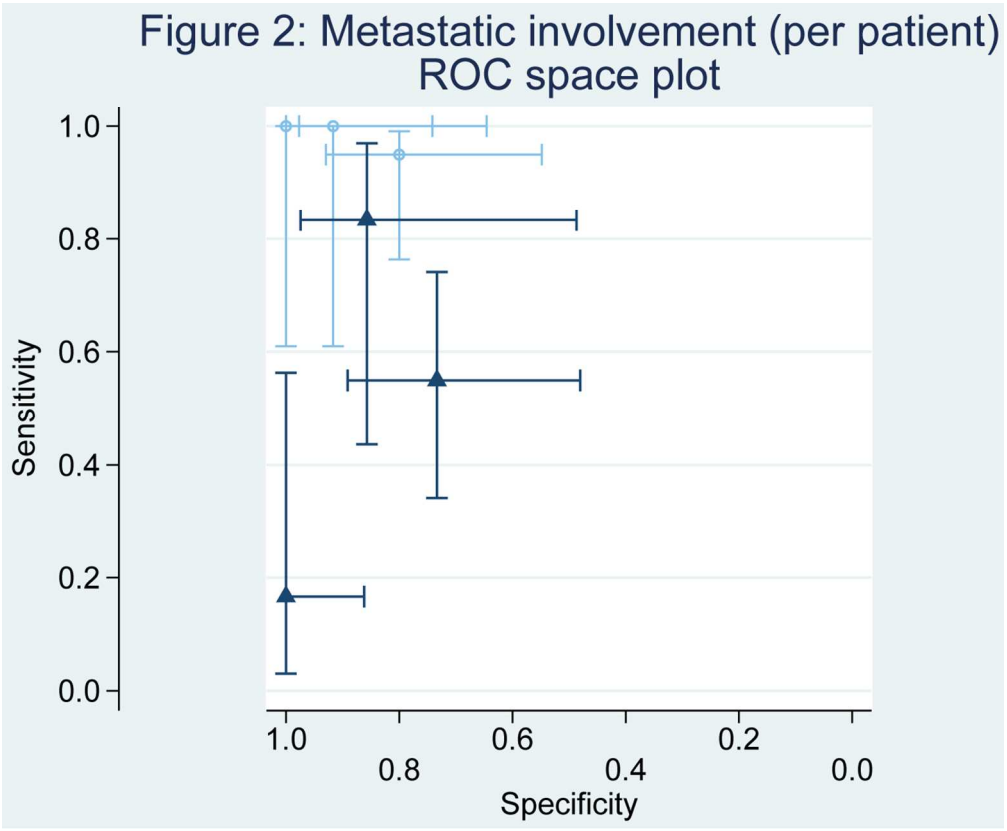

Figure 2: Metastatic involvement (per patient): ROC space plot.

Light blue denotes PET CT
Dark blue denotes conventional imaging
115x95mm (300 x 300 DPI)

Appendix 1 Searching

Databases searched for studies of FI for RMS
• MEDLINE and MEDLINE In-Process (via Ovid, 1946 to present, searched 30/October/2013); • CENTRAL (***Cochrane Central*** Register of Controlled Trials) (via Cochrane Library. CENTRAL issue 9 of 12 September 2013. Searched 30/October/2013); • Clinical Trials.gov (via http://clinicaltrials.gov/, Searched 14/November/13) • EMBASE (Excerpta Medical Database) (via OVID SP 1974 to 2013 October 29>, searched 30/October/13); • HTA database (via CRD website: http://www.crd.york.ac.uk/crdweb/HomePage.asp, searched 31/October/13) • International Cancer Research Partnership (ICRP) (via https://www.icrpartnership.org/database.cfm, searched 14/November/13) • metaRegister of Controlled Trials (mRCT) active registers (via http://www.controlled-trials.com/mrct/search.html , searched 11/November/13) • PubMed (via http://www.ncbi.nlm.nih.gov/pubmed/advanced, searched 08/November/13)
Databases searched for systematic reviews of FI for cancer
• CDSR (***Cochrane Database of Systematic Reviews***) (via Cochrane Library. CDSR issue 11 of 12 November 2013. Searched 05/November/2013) • DARE – Database of Abstracts of Reviews of Effects (via CRD website, http://www.crd.york.ac.uk/CRDWeb/. Searched 05/November/13)

Searches for studies of functional imaging for RMS:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Searched 30-10-2013

Annotated search strategy:

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1 Rhabdomyosarcoma, Alveolar/ or Rhabdomyosarcoma/ or Rhabdomyosarcoma, Embryonal/ (9170)

2 Rhabdomyosarcoma*.ti,ab. (9377)

3 1 or 2 (12196)

Line 3 captures terms for rhadomyosarcoma (RMS)

4 positron-emission tomography/ or "positron-emission tomography and computed tomography"/ (31876)

5 (photon emission adj3 tomograph*).ti,ab. (14192)

6 (positron emission adj3 tomograph*).ti,ab. (36244)

7 pet.ti,ab. (54796)

8 spect.ti,ab. (20595)

9 Fluorodeoxyglucose F18/ (18591)

10 Fluorodeoxyglucose.ti,ab. (8878)

11 (18-fdg or fdg-18 or 18f-fdg or fdg-18f).ti,ab. (5551)

12 (18fdg or fdg18 or 18ffdg or fdg18f).ti,ab. (758)

13 or/4-12 (95736)

Line 13 captures terms for Positron Emission Tomography (PET)

14 3 and 13 (112)

Line 14 combines terms for PET and RMS

15 magnetic resonance imaging/ or diffusion magnetic resonance imaging/ or diffusion tensor imaging/ (295995)

16 magnetic resonance imag*.ti,ab. (141536)

17 (MRI or MRIs).ti,ab. (142279)

18 (MR or MRs).ti,ab. (119271)

19 (diffusion adj4 (imag* or tractograph*)).ti,ab. (16385)

20 magnetic resonance tractograph*.ti,ab. (32)

21 or/15-20 (430131)

Line 13 captures terms for Magnetic Resonance Imaging (MRI)

22 21 and 3 (561)

Line 22 combines terms for MRI and RMS

23 magnetic resonance spectroscopy/ or electron spin resonance spectroscopy/ or nuclear magnetic resonance, biomolecular/ (182753)

24 spectroscop*.ti,ab. (228032)

25 nuclear magnetic resonance.ti,ab. (30681)

26 nmr*.ti,ab. (122382)

27 or/23-25 (354880)

Line 27 captures terms for spectroscopy

28 27 and 3 (49)

Line 28 combines terms for spectroscopy and RMS

29 dcemri*.ti,ab. (30)

30 functional imag*.ti,ab. (7644)

31 or/29-30 (7672)

Line 31 captures terms for functional imaging

32 31 and 3 (3)

Line 32 combines terms for functional imaging and RMS

33 14 or 22 or 28 or 32 (666)

Line 33 brings together all the records identified for the various different types of ffunctional imaging

CENTRAL (Cochrane Central* Register of Controlled Trials*) (via Cochrane Library. CENTRAL issue 9 of 12 September 2013. Searched 30/October/2013);

Search strategy:

#1 [mh ^"Rhabdomyosarcoma, Alveolar"] or [mh ^"Rhabdomyosarcoma, Embryonal"] or [mh ^Rhabdomyosarcoma] in Trials 51

#2 Rhabdomyosarcoma* in Trials 90

#3 {or #1-#2} 90

Clinical Trials.gov (via http://clinicaltrials.gov/, **Searched 14/November/13)**

Search strategy:

rhabdomyosarcoma* and (tomograph* OR PET* OR SPECT* OR “magnetic resonance*” OR MRI OR MRIs OR spectroscop* or “functional imag* or Fluorodeoxyglucose” OR dcemri*) – 10 records

EMBASE (*Excerpta Medical Database*) (via OVID SP 1974* to 2013 October 29*>, searched 30/October/13)

Search Strategy:

---

1 rhabdomyosarcoma/ or embryonal rhabdomyosarcoma/ (13925)

2 Rhabdomyosarcoma*.ti,ab. (11270)

3 or/1-2 (16101)

4 positron emission tomography/ (80086)

5 computer assisted emission tomography/ (16482)

6 (photon emission adj3 tomograph*).ti,ab. (16812)

7 (positron emission adj3 tomograph*).ti,ab. (44186)

8 pet.ti,ab. (80248)

9 spect.ti,ab. (29923)

10 Fluorodeoxyglucose F18/ (33010)

11 Fluorodeoxyglucose.ti,ab. (11286)

12 (18-fdg or fdg-18 or 18f-fdg or fdg-18f).ti,ab. (11612)

13 (18fdg or fdg18 or 18ffdg or fdg18f).ti,ab. (1984)

14 or/4-13 (156421)

15 14 and 3 (309)

16 nuclear magnetic resonance imaging/ or diffusion tensor imaging/ or diffusion weighted imaging/ (459617)

17 magnetic resonance imag*.ti,ab. (161366)

18 (MRI or MRIs).ti,ab. (199744)

19 (MR or MRs).ti,ab. (131475)

20 (diffusion adj4 (imag* or tractograph*)).ti,ab. (20139)

21 magnetic resonance tractograph*.ti,ab. (36)

22 or/16-21 (571190)

23 22 and 3 (1229)

24 nuclear magnetic resonance spectroscopy/ (98107)

25 electron spin resonance/ (32873)

26 spectroscop*.ti,ab. (232789)

27 nuclear magnetic resonance.ti,ab. (32396)

28 nmr*.ti,ab. (141440)

29 or/24-28 (386947)

30 3 and 29 (71)

31 dcemri*.ti,ab. (80)

32 functional imag*.ti,ab. (9444)

33 or/31-32 (9518)

34 33 and 3 (8)

35 15 or 23 or 30 or 34 (1432)

HTA database (via CRD website: http://www.crd.york.ac.uk/crdweb/HomePage.asp, searched 31/October/13)

Search strategy:

1) MeSH DESCRIPTOR Rhabdomyosarcoma EXPLODE ALL TREES IN HTA 0 hits

2) ((rhabdomyosarcoma*)) and (Project record:ZDT OR Full publication record:ZDT) 1 hit

3) #1 OR #2 1 HIT

International Cancer Research Partnership (ICRP) (via https://www.icrpartnership.org/database.cfm, searched 14/November/13)

Search strategy:

Containing All of These Words: Rhabdomyosarcoma*
Funding Years: 2013, 2012, 2011, 2010, 2009, 2008, 2007, 2006, 2005, 2004, 2003, 2002, 2001, 2000
CSO Codes:

- 4.1 - Technology Development and/or Marker Discovery
- 4.2 - Technology and/or Marker Evaluation with Respect to Fundamental Parameters of Method
- 4.3 - Technology and/or Marker Testing in a Clinical Setting
- 4.4 - Resources and Infrastructure Related to Early Detection, Diagnosis or Prognosis

17 hits

metaRegister of Controlled Trials (mRCT) active regsiters (via http://www.controlled-trials.com/mrct/search.html **, searched 11/November/13)**

Search strategy:

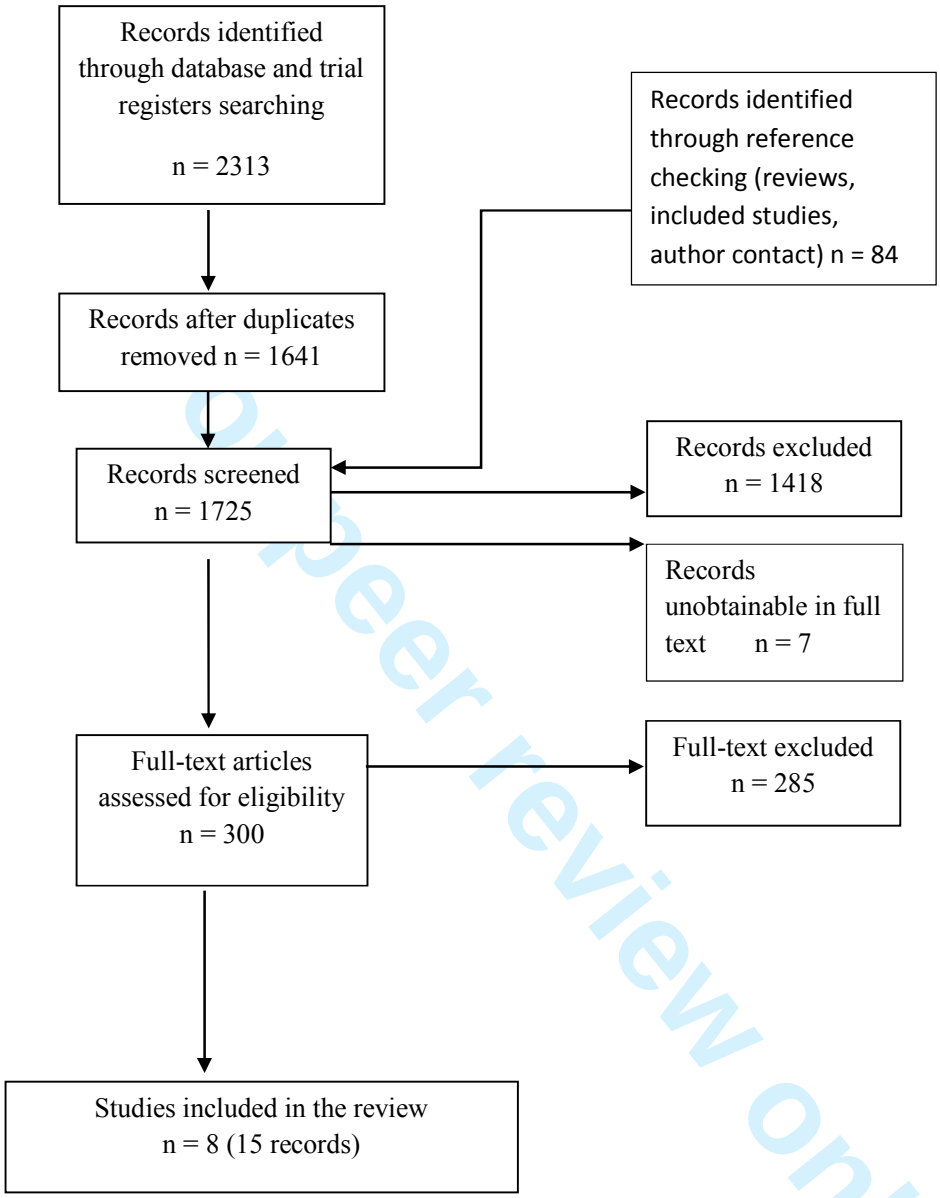
Rhabdomyosarcoma* in all databases 46 hits

PubMed (via** http://www.ncbi.nlm.nih.gov/pubmed/advanced**, searched 08/11/13)

Search strategy:

#1	Search rhabdomyosarcoma[MeSH Terms]	8930
#2	Search Rhabdomyosarcoma, Alveolar[MeSH Terms]	558
#3	Search Rhabdomyosarcoma, Embryonal[MeSH Terms]	702
#4	Search Rhabdomyosarcoma*[Title/Abstract]	9174
#5	Search (#1 or #2 or #3 or #4)	11962
#9	Search "Positron-Emission Tomography"[Mesh] OR "Positron-Emission Tomography and Computed Tomography"[Mesh]	28349
#10	Search ("photon emission" AND tomograph*[Title/Abstract])	14403
#11	Search (positron emission AND tomograph*[Title/Abstract])	36210
#12	Search pet[Title/Abstract]	53207
#13	Search spect[Title/Abstract]	20474
#15	Search "Fluorodeoxyglucose F18"[Mesh]	17448
#16	Search Fluorodeoxyglucose[Title/Abstract]	8566
#20	Search ("18-fdg" or "fdg-18" or "18f-fdg" or "fdg-18f"[Title/Abstract])	5387
#22	Search ("18fdg" or "fdg18" or "18ffdg" or "fdg18f"[Title/Abstract])	702
#30	Search magnetic resonance imag*[Title/Abstract]	134446
#31	Search (MRI or MRIs[Title/Abstract])	371243
#32	Search (MR or MRs[Title/Abstract])	120807
#35	Search ((diffusion AND imag*) or (diffusion AND tractograph*)[Title/Abstract])	0
#36	Search magnetic resonance tractograph*[Title/Abstract]	28
#37	Search ("magnetic resonance spectroscopy"[Mesh] OR "nuclear magnetic resonance, biomolecular"[Mesh] OR "electron spin resonance spectroscopy"[Mesh] OR "nuclear magnetic resonance, biomolecular"[Mesh])	172389
#38	Search spectroscop*[Title/Abstract]	225674
#39	Search nuclear magnetic resonance[Title/Abstract]	29424
#40	Search nmr*[Title/Abstract]	118295
#41	Search dcemri*[Title/Abstract]	26
#42	Search functional imag*[Title/Abstract]	6839
#43	Search ((#9 or #10 or #11 or #12 or #13 or #15 or #16 or #20 or #22 or #30 or #31 or #32 or #36 or #37 or #38 or #39 or #40 or #41 or #42))	848762
#44	Search (#5 and #43)	663

Figure 1 Flow of studies through the review



Appendix 2: Quality assessment

Study Assessment tool

Possible answers for each criterion were “yes”, “no”, and where relevant, “unclear”, or “not applicable”.

- Were the selection/eligibility criteria adequately reported?
- Is the sample likely to be representative?
- Were patients recruited prospectively?
- Were patients recruited consecutively?
- Was the participation rate adequate (>80% of those eligible)
- Was there at least 80% follow-up from baseline?
- Was loss to follow-up reported?
- Were relevant prognostic factors reported? (e.g. histology, location of primary tumour)
- Were other relevant confounding factors reported? (e.g. excisional biopsy, variations in timing of imaging including variations in treatment point when imaging took place)
- Was an appropriate measure of variability reported?
- Was there an appropriate statistical analysis?
- Were there any other important limitations?
- Were the FI results assessed blind to the reference standard?
- Were the FI results assessed blind to the results of CI?
- Were there two independent assessors?

Intervention assessment criteria

Possible answers for each criterion were “yes”, “no”, and where relevant, “unclear”, or “not applicable”.

- Was the same scanner used for baseline and follow-up?
- Was residual activity in the syringe and injection tubing measured to accurately determine administered dose?
- Was an appropriate uptake time used (baseline minimum 60 minutes; baseline ± 10 minutes at follow-up)?
- Were acquisition technique and reconstruction parameters maintained for baseline and follow up; was the same CT protocol used?
- Were serum glucose and average liver SUV recorded before each PET?
- Were all patients weighed before imaging, at facility, using calibrated scale?
- Were dose calibrators calibration maintained and dose calibrator clocks synchronised with scanner clocks?
- Were screensaves or other documentation used to improve reproducibility in defining regions of interest between baseline and follow-up?

Results of study quality assessment

Study	Selection criteria	Representative sample	Prospective recruitment?	Consecutive recruitment?	Adequate participation?	Adequate retention?	Loss to follow up?	Prognostic factors reported?	Confounding factors reported?	Appropriate measures of variability?	Appropriate statistical analysis?	Blind to ref standard	Blind to CI	Two assessors?
Baum (2011)[36]	yes	unclear	no	unclear	unclear	yes	yes	yes	yes	yes	yes	no	unclear	yes
Dharmarajan (2012)[46]	yes	unclear	no	unclear	unclear	yes	yes	yes	yes	yes	yes	unclear	unclear	unclear
Eugene (2012)[38]	yes	yes	unclear	yes	yes	no	yes	yes	yes	yes	yes	unclear	yes	yes
Federico (2012)[40]	yes	yes	no	unclear	unclear	NA	NA	yes	yes	yes	yes	yes	yes	no
Klem (2007)[43]	yes	unclear	no	no	yes	yes	unclear	yes	no	no	no*	unclear	unclear	unclear
Ricard (2011)[15]	yes	Yes ^	no	unclear	unclear	yes	yes	yes	yes	no	no	unclear	yes	yes
Tateishi (2009)[16]	yes	unclear	no	unclear	unclear	yes	yes	yes	yes	yes	yes	yes	yes	yes
Volker (2007)[35]	yes	unclear	yes	unclear	unclear	NA	NA	no	yes	yes	yes	yes	yes	yes

**Those who had had chemotherapy and those who had not were analysed together. ^ but note atypical histology/gender balance*

Intervention quality

Study	Same scanner used?	Administered dose accuracy?	Uptake time appropriate?	Acquisition technique/reconstruction parameters maintained?	Serum glucose and average liver SUV	Patient weighed	Adequate calibration	Reproducibility of ROI
Baum (2011)[36]	NA	unclear	yes	NA	yes	unclear	unclear	unclear
Dharmarajan (2012)[46]	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear
Eugene (2012)[38]	unclear	unclear	yes	yes	unclear	unclear	unclear	Unclear*
Federico (2012)[40]	NA	unclear	yes	NA	unclear	unclear	unclear	unclear
Klem (2007)[43]	NA	unclear	No‡	NA	unclear	unclear	unclear	unclear
Ricard (2011)[15]	unclear	unclear	yes	unclear	unclear	unclear	unclear	unclear
Tateishi (2009)[16]	NA	unclear	yes	NA	unclear	unclear	unclear	unclear
Volker (2007)[35]	NA	unclear	unclear	unclear	unclear	unclear	unclear	unclear

**Blood glucose level was controlled but it is unclear if average liver SUV was recorded before each PET.‡45 to 60 minutes*

Appendix 3: Results of imaging of primary tumours

Study	Image	N	Primary tumour imaging details	SUV_{max}: mean (range)
Baum (2011)[36]	PET-CT	41		CRG2: 3.7 (SD 1.9)(N =11) CRG3: 3.6 (SD 2.3) (N = 18) CRG 4: 5.2 (SD 3.2) (N = 12)*
Dharmarajan (2012)[46]	PET-CT	94		7.0 (median) (0 to 31)(N =58)
Eugene (2012)[38]	PET-CT	23	PET detected 17/18 tumours; CI detected 18/18; (4 sites were completely excised before imaging, 1 was not clearly identified at diagnosis)	6.2(median) (2.7-15.4)
Federico (2012)[40]	PET-CT	30	PET detected all 21 tumours (8 completely excised before imaging; 1 unknown primary)	7.2 (2.5 to 19.2) (N = 18)
Klem (2007)[43]	PET	24	23 tumours evaluated (1 previously completely excised)	Initial staging: 7.7 (4.1 to 12.7) 1-13 days post-chemotherapy (first dose): 4.7 (2.4 to 8.4)
Ricard (2011)[15]	PET-CT	13	PET-CT detected 11/11 tumours including previously occult primary; CI detected 10/11. 2 patients had prior surgery; both PET and CI missed 1 microscopic residual lesion. Follow-up (N = 8) PET and CI both detected 3 residual local disease cases and 4 clear results. PET clear for 1 patient with positive CI; PET result confirmed true negative by follow-up.	Initial staging: 3.7 (median) (2 to 6.9) Follow-up (N = 8) 5.8 (median) (5.2-6.1)
Tateishi (2009)[16]	PET-CT	35	Both PET-CT (using CT component) and CI correctly classified the T stage in all patients	NR
Volker (2007)[35]	PET	46 (11 RMS)	Both PET and CI detected all primary tumours	7.0 (SD 3.4)

CRG clinical risk group; SD standard deviation *all figures are mean SUV_{max}/SUV_{liver}

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2, Table 1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1,2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Table 1 P3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P3, Appendix
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P2, Fig 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P3, Appendix
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P3

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	P3

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P4, appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P3, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P4-6, Figs 2+3, tables 3-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A but see figs 2+3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P6-7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P6-7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P6-8
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P8

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An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: Systematic review.

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An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: Systematic review.

Abstract

Purpose/Objective: Rhabdomyosarcoma (RMS) management depends on risk stratification at diagnosis and treatment response. Assessment methods include CT, MRI, bone scintigraphy, histological analysis and bone marrow biopsy. Advanced functional imaging (FI) has potential to improve staging accuracy and management strategies.

Materials and Methods: We conducted a systematic review (PROSPERO 2013:CRD42013006128) of diagnostic accuracy and clinical effectiveness of FI in histologically proven paediatric RMS. PRISMA guidance was followed. We searched 10 databases to November 2013. Studies with ≥10 RMS patients which compared PET, PET-CT or DWI MRI to conventional imaging at any treatment stage were included. Study quality was assessed. Limited, heterogeneous effectiveness data required narrative synthesis, illustrated by plotting sensitivity and specificity in ROC space.

Results: Eight studies (six PET-CT, two PET) with 272 RMS patients in total were included. No DWI-MRI studies met inclusion criteria. Pooled estimates were not calculated due to sparseness of data. Limited evidence indicated initial PET-CT results were predictive of survival. PET-CT changed management of 7/40 patients. Nodal involvement PET-CT: sensitivity ranged from 80% to 100%; specificity from 89% to 100%. Distant metastatic involvement: PET-CT sensitivity ranged from 95% to 100%; specificity from 80% to100%. Data on metastases in different sites were sparse. Limited data were found on outcome prediction by PET-CT response.

Conclusions: PET/PET-CT may increase initial staging accuracy in paediatric RMS, specifically in the detection of nodal involvement and distant metastatic spread. There is a need to further assess PET-CT for this population, ideally in a representative, unbiased and transparently selected cohort of patients.

Article Summary: Strengths and limitations of this study

- This is the first systematic review of the use of advanced functional imaging in the management of rhabdomyosarcoma in children and young people.
- No studies of DWI-MRI in managing rhabdomyosarcoma of sufficient quality for inclusion were identified.
- Rigorous methodology identified the limitations of the existing research supporting this use of PET/PET-CT in the staging, prognosis development and outcome assessment of diagnosed RMS.
- Paucity of evidence prevented meta-analysis of sensitivity and specificity and contributed to considerable uncertainty around the true value of PET-CT, including whether it should be considered as an additional or a replacement diagnostic tool.
- Potential benefits of PET-CT in increasing staging accuracy were identified: specifically identification of nodal involvement and metastatic spread. Clear research recommendations for incorporation of PET-CT into future treatment trials are presented.

Background

Rhabdomyosarcoma (RMS) accounts for over 50% of sarcomas in children and young people. (1) (2) Incidence is 4.6 per million aged < 20 years. RMS frequently presents as a soft-tissue mass. The commonest sites of origin are head and neck, genitourinary tract, and limbs. Treatment is based on a multimodality approach including neoadjuvant chemotherapy, surgery where possible, radiotherapy, and adjuvant chemotherapy. Overall outcomes have improved but remain suboptimal, with three-year event-free survival (EFS) rates for patients with localised disease of around 60% in Europe and a corresponding overall survival (OS) of 80%.(3, 4) Patients who present with metastatic disease have much poorer prognoses and should be considered for novel treatment strategies. Correct staging is imperative.

Current treatment protocols rest on decisions at several points during therapy. Full initial staging employs cross-sectional imaging of the primary tumour (often with MRI); further cross-sectional imaging of the chest, abdomen, and pelvis; a radiolabelled bone scan; and pelvic bone marrow biopsies. These methods are also used to assess disease response for treatment modification and at the end of treatment as ongoing surveillance.(3) The usefulness of assessment methods is under ongoing evaluation; a recent European paediatric Soft tissue Sarcoma Group (EpSSG) analysis showed that otherwise low risk patients are unlikely to have isolated bone metastasis; in future bone scans may be omitted for these patients.(5) . Current assessment methods give discordant results at post-chemotherapy evaluation, highlighting the potential importance of functional imaging (FI).(6)

FI has been incorporated into management of other malignancies (e.g. staging non-small-cell lung cancer (NSCLC) and assessing treatment response in Hodgkin lymphoma) after extensive reviews found strong evidence for PET-CT.(7) It was found to be cost-effective for assessment of recurrent colorectal cancer,(8) but was less useful than non-nuclear technologies (e.g. functional MRI and nodal biopsies) in regional node evaluation in breast cancer.(9) Previous systematic reviews with meta-analysis of sarcomas generally have found uncertain and heterogeneous results.(10, 11)

This is the first systematic review of FI in children and young people with RMS diagnosis. FI has potential as an additional imaging technique or replacement for current imaging modalities for initial staging and/or response assessment.

Objective

To assess the role of FI (PET/PET-CT and DWI-MRI) in the management of RMS in childhood and adolescence and to consider its potential as a tool for improving both diagnostic (staging) and prognostic evaluation. Assessment of FI for treatment response and end of treatment evaluations were secondary aims. The review was not designed to assess the differential diagnosis of RMS in patients with suspected sarcoma.

Methods

We undertook a systematic review of the diagnostic accuracy and clinical effectiveness of PET, PET-CT and DWI MRI for assessment of histologically proven RMS in children and young people. The protocol was registered on PROSPERO (2013:CRD42013006128)(12) and PRISMA guidance adhered to. We consulted three public patient (PPI) representatives while writing the protocol and they contributed to the selection of outcomes assessed.

We searched 10 databases (including MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) from inception to November 2013 without restrictions on publication status, date or language (see appendix 1 for full list of databases and complete search strategies).

The following prespecified inclusion criteria were applied:

- **Participants**: Children and young people aged 0 to 24 years of age who are diagnosed with histologically proven RMS of any type. Studies with mixed tumour types will be included if outcome data for RMS patients are reported separately for at least one outcome. Studies with mixed populations of children/young people and adults were included where it was clear that a majority of patients were children/young people.
- **Interventions:** FI: PET +/- CT, or DWI-MRI used at any point in the management of RMS
- **Comparator:** Conventional imaging (One or more of contrast-enhanced CT or standard MRI, Technetium-99m bone scintigraphy)
- **Primary outcome:** EFS or OS at any time point.
- **Secondary outcomes:** Relapse rates, quality of life, adverse events or acceptability of the technology (by patient, carer or health professional), histological confirmation via lesional biopsy, or independent imaging or comparative classification of staging and risk classification of disease and treatment alteration in the light of imaging tests performed
- **Study design:** Prospective and retrospective studies of any design with at least 10 RMS patients for whom separate data is available for at least one outcome (following a protocol amendment due to lack of data; originally studies were required to include ≥ 20 RMS patients).

Studies were assessed for inclusion and appraised for quality by two independent reviewers. We used a tool adapted from previous Health Technology Assessment (HTA) reviews(13, 14) for quality assessment of case series. We also assessed the reliability of the processes followed in carrying out PET and the degree to which accepted guidelines for the semi-quantification using standardised uptake values were followed.(15)

Data were extracted onto a prespecified form using the package EPPI-Reviewer 4 from the UK EPPI-Centre by one researcher and checked by a second (forms were piloted by two independent researchers). A third researcher was consulted where necessary. Patient-level data were extracted to enable construction of 2x2 tables for detection of nodal involvement and distant metastases. Sensitivity and specificity of PET and conventional imaging were calculated for each study and plotted in ROC space using the METANDI package in STATA. There were insufficient data to calculate pooled sensitivity and specificity.

At all stages of the review process we attempted to contact study authors about uncertain, missing or incomplete data.

Due to the limited and incomplete nature of the data reported, data at the level of individual primary, nodal or metastatic sites were summarised in a narrative synthesis. Data on survival, tumour response and treatment modification were very limited and heterogeneous so were also summarised narratively.

Results

Quantity and quality of evidence

We identified 1725 unique records and assessed 300 as full-text papers. Six studies of PET-CT(16-21) and two of PET(22, 23) were included; these were reported in a total of 15 publications(16-30) and the most up-to-date data were used in the review (see Appendix for flow diagram). All studies had a full primary English publication; in one case, survival data were available only in abstract.(29)

Seven studies included only RMS patients;(16-19, 21-23) one included a minority of RMS patients with separate data.(20) Data were reported on a total of 272 RMS patients. Two additional studies reported in abstract included >10 RMS patients but were excluded as, despite author contact, we were unable to obtain separate RMS patient data.(31, 32) One study reported separate RMS data only for the subset of patients with a primary tumour in the extremities and was included because of this data.(20) Three studies included one or more adults aged ≥25 years; these studies were included because it was clear that the great majority of patients were children/young people; median ages were 11 and 13 in two studies(17, 23) and the mean age in the third was 19.8.(19)

No studies of DWI-MRI met inclusion criteria (even after protocol amendment from >20 cases to >10 cases); only studies that assessed it for differential diagnosis with very few RMS cases were found.(33-39) These studies of DWI are discussed elsewhere. [Norman et al, Paed Radiol, in press 2014] A full list of excluded studies is available on request.

All studies used fludeoxyglucose (fluorodeoxyglucose,18F) as the radiopharmaceutical for PET. Most studies reported using all possible conventional imaging techniques as a comparator to PET or PET-CT (see table 2). The reference (gold) standard (as distinct from the comparison with conventional imaging) was typically a mixture of histopathology, clinical examination and follow-up.

Included studies often involved more children with unfavourable prognoses than would be expected in clinical practice: 52% of the patients in the series had an unfavourable, alveolar histology compared to 20-30% in clinical practice.(1) Histology was generally not well described and information on genetic predispositions was limited to one study which noted that no patient had a history of familial cancer syndrome. (21) Where reported, large numbers of patients had stage III or IV disease compared to around 15% with stage IV disease in clinical practice.(40) Several studies included higher numbers of patients with primary tumours of the extremities. Study characteristics are summarised in Table 1.

[table 1 about here]

All studies were opportunistic case series. Most were retrospective and did not comprise consecutive series of patients. It was often unclear how representative of the eligible population the included patients were. Details of FI procedures were often not reported. See Appendix 2 for a summary of quality assessment results. Outcome reporting was inconsistent and often incomplete. In some cases was this remedied by contacting authors.

Survival and related outcomes

Only one study (N=41) reported data on overall survival (OS).(22) This found that metabolic activity of the primary tumour on PET-CT had prognostic significance for survival (p=0.007). Also predictive of survival were PET-CT detection of nodal involvement (P=0.016), PET-CT detection of metastases

(P=0.002), and a composite outcome (PET group; P=0.002). Dichotomisation around the point SUV_{max}/SUV_{liver} = 4.6 was also predictive (P=0.002). Nodal and metastatic involvement retained statistical significance in a multivariate analysis; primary tumour intensity did not.

Three studies reported data on event-free survival (EFS).(17, 22, 29) One (N=41) found similar results for EFS as for OS, with prognostic significance for primary tumour intensity (P=0.005), lymph node detection (P=0.008), and metastases detection (P=0.01). Dichotomisation around the point SUV_{max}/SUV_{liver} = 4.6 did not predict EFS.(22) Another study (N=94) reported trends towards prognostic significance for PET-CT results dichotomised by SUV_{max} = 7.0 at initial staging (P=0.08) and by pre-RT PET-CT-positivity (after median 15 weeks chemotherapy) (P=0.06).(17) At post-RT assessment PET-CT-negative patients were significantly less likely to relapse than PET-positive individuals (P=0.02). The third study (N=38), available as an abstract, reported no prognostic significance of PET-CT at any point.(29) None of these reports demonstrated an additional prognostic value of metabolic activity indices above conventional prognostic criteria.

One study reported tumour response.(16) In a subset of 13 patients PET-CT was more likely than conventional imaging to show complete response to treatment; most of these patients were assessed by conventional imaging as having a partial response and twelve were in remission at follow-up.

Treatment alteration

PET-CT changed the management or treatment course of 7/40 patients in studies that reported this outcome.(16, 20, 21)

Quality of life and acceptability

There were no data on quality of life or acceptability of the technology. All three PPI representatives considered that additional scans (and their associated requirements of time, travel, and additional procedures) were worthwhile if they could provide additional information to inform the treatment plan and/or prognosis.

Diagnostic data

Lymph nodes

For nodal involvement, PET-CT or PET showed sensitivity of 80% (1 study)(18) or 100% (3 studies)(19-21) and specificity of 89% to 100% at the patient level. This compared to sensitivity of between 67% and 86% and specificity of 90% or 100% for conventional imaging (Table 2 and Figure 2). The ROC space 'cross-hairs' plots show each study's estimates of sensitivity and specificity as a marker at the point estimate, with 95% confidence intervals demonstrated by lines. In reading such graphs, tests with better discriminatory ability fall in the top left corner of the plot, and non-discriminatory tests fall on a 45° line between the bottom left and top right.(41)

[Table 2 about here]

[Figure 1 about here]

Nodal level data from three studies also indicated that PET-CT was able to detect more positive nodes than conventional imaging with very few false positives.(16, 18, 21) One study with fully

reported data found sensitivity and specificity of 100% for PET-CT compared to 75% and 94% for conventional imaging. (16) Where reported, PET-CT generated many fewer indeterminate results (1 versus 18/35) and more true negatives than conventional imaging .(18)

Distant metastases

For detection of distant metastatic sites, PET-CT had a sensitivity of 95% (1 study)(19) or 100% (2 studies)(18, 21) and specificity of 80% to 100% at the patient level. This compared to sensitivity of between 17% and 83% and specificity of between 43% and 100% for conventional imaging (Table 2 and Figure 2).

[Figure 2 about here]

Site level data from another study also found higher sensitivity and specificity (100% and 96%) for PET-CT compared to 66% and 91% for conventional imaging.(16)

Information on detection of metastases in different sites was extremely limited and reported at the level of individual cases (Table 3).(16, 18, 19, 21) There were indications from this very limited evidence base that PET-CT may be superior to CI for detection of bone lesions, in that both additional lesions and patients with otherwise undetectable bone involvement were identified. (16, 18, 19, 21) The number of false positives was low. PET-CT may also have potential to specifically identify marrow involvement in some patients but this finding is unclear and based on tiny numbers of patients; sensitivity appeared limited. (18) PET-CT appeared poor for detection of lung metastases.(18, 21) There were indications that PET-CT may perform better than conventional imaging in detecting soft tissue lesions in non-pulmonary locations,(18, 19) possibly including distal nodal involvement. (21)

[Table 3 about here]

Primary tumours

The ability of PET-CT to detect primary tumours was good; only one known tumour site was missed(16) and one previously occult primary was identified;(21) further details are in Appendix 3.

Discussion

We identified eight studies (272 patients) of PET or PET-CT in children and young people with RMS and no eligible studies of DWI-MRI.

The studies identified had multiple limitations. All studies were opportunistic case series open to a range of biases. As such they addressed multiple aspects of the use of PET in RMS management. Patients already had a diagnosis of RMS so the studies were not diagnostic in the conventional sense; rather they were concerned with accuracy of staging, determination of prognosis and, in some cases, evaluation of treatment outcome. The review was not designed to assess the value of PET-CT in imaging primary tumours, as the requirement for histologically proven RMS diagnosis meant that almost all patients had a known tumour site. This makes comparison to earlier reviews that included all sarcomas unhelpful.(10)

The studies included a higher proportion of more challenging cases than expected in clinical practice. Imaging methodology was not well reported. Duplicate blinded evaluation of the FI results relative

to the conventional imaging results or reference standard was often absent or unclear. Results were often not clearly or fully reported and data remained inconsistent and incomplete even after contacting authors. Our findings are therefore tentative and require confirmation by further research.

PET-CT was consistently somewhat better than conventional imaging at identifying patients with nodal involvement at initial staging and was clearly more sensitive to individual positive nodes, with fewer indeterminate results. PET-CT appeared to improve sensitivity in identification of distant metastases including identifying patients in whom distal metastatic involvement was not otherwise indicated. There is a suggestion of a role for PET-CT in detection of bone involvement but a great deal of uncertainty. Data for lung lesions are sparse and do not suggest utility. These results accord with reviews of PET-CT in staging of osteosarcoma(42) and PET in general diagnosis of pulmonary nodules.(43)

There is very limited evidence on use of PET-CT for treatment response and end of treatment evaluation. Only three studies investigated the primary outcome of survival and one evaluated tumour response. PET-CT at initial staging may have predictive value for OS and EFS. The role of PET-CT in the assessment of treatment response before and after radiotherapy is unclear. PET-CT may be superior at ascertaining complete response to chemotherapy but this is based on one small study. The tentative findings of this review suggest that the performance of PET-CT in RMS may be closer to that in Hodgkin lymphoma, NSCLC(7) and colorectal cancer(8) than in breast cancer.(9)

None of the studies reported data on the impact of FI or conventional imaging on quality of life or acceptability to any identified stakeholder group. Our PPI representatives indicated that potential additional information was highly valued and mattered more than a need for additional procedures and the resource implications of additional scans. They were particularly supportive of FI in further research with potential to clarify possible benefits of additional or alternative imaging procedures.

This systematic review represents the first thorough evaluation of the international evidence on FI in the management of childhood and adolescent RMS. Extensive searching without language restrictions ensured the inclusion of all relevant studies. We made substantial efforts to obtain supplementary data from authors. Although some studies contained patients aged >24 years we are confident from the mean/median ages reported that these were a small minority of the populations and that the relevance of the studies to the paediatric population was not significantly impacted. Excluding these studies would have resulted in the loss of data on a significant proportion of documented PET use in paediatric RMS. Studies were quality assessed and synthesised to provide an unbiased comprehensive assessment of the evidence

The key limitation was our inability to obtain all relevant data despite contacting authors. In particular we are aware of two case series in sarcoma patients which included >10 RMS patients that we could not include as authors were unable to provide separate data on RMS cases. The lack of complete patient-level data from all included studies meant we were unable to calculate pooled estimates for the sensitivity and specificity of FI and conventional imaging. However, even had we acquired full data on all known paediatric RMS patients, the total number would have remained under 300. Any answers to the review questions would have remained tentative and uncertain. There is an urgent need for more reliable disease assessment at all stages of RMS management. PET-

CT may be an option for this with sufficient prospective testing through incorporation into any future trials of RMS treatments.

Conclusion

This review highlights potential from PET-CT in imaging of children and adolescents with RMS but there is a high level of uncertainty in these data and their relevance to clinical practice. Limited evidence suggests that PET / PET-CT has potential to increase initial staging accuracy, specifically detection of nodal involvement and distant metastatic spread. There is little evidence on the impact of PET-CT in assessment of therapeutic response or post-treatment assessment. The ultimate impact of FI with PET-CT on treatment outcomes could not be addressed and it remains unclear whether and how increasing accuracy at initial staging might alter patient management and survival. It was impossible to determine whether PET-CT could replace any current imaging tests or should be used as an adjunct.

DWI-MRI has been insufficiently researched to answer questions of utility in RMS; the very limited evidence base for this is discussed elsewhere (Norman et al; Paed radiol 2014; in press).

Recommendations for further research.

- A representative, unbiased, and transparently selected cohort of patients (entering a treatment RCT) should be identified. All patients should be evaluated using PET-CT as an adjunct to conventional techniques at initial staging, treatment response, and end of treatment.
- The protocol should specify interim data analysis, potentially enabling PET-CT to replace one or more conventional staging techniques or substantially modify treatment delivery by response assessment.
- Results should be fully reported and individual patient data made available.
- Methodology of the PET-CT process should be standardised and reported fully. This should include independent reading of scans by multiple assessors blinded to conventional imaging and clinical/histological results.
- Appropriate qualitative methodologies should be used to assess the additional burden of treatment to patients and healthcare system, and resource use prospectively evaluated.
- Further comparative research on DWI-MRI in RMS is needed; researchers using this technology in RMS patients should be encouraged to publish case series in the first instance.

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Author contributions: BP Designed concept for study, wrote initial draft of protocol, supervised review, undertook analysis, reviewed and edited manuscript; GN Contributed to protocol, screened and assessed all papers, developed and conducted data extraction, wrote initial and edited later drafts of manuscript; DF: Contributed to protocol, screened and assessed all papers, developed and conducted data extraction, reviewed and edited the manuscript; KL designed and undertook the search strategy, managed the study database and reviewed and edited the manuscript; JC, MJ, SG,

DL, HM, KM contributed to the protocol, provided clinical advice to the review, reviewed and edited the manuscript.

[3670 words]

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Table 1: Participant characteristics

Study	Intervention [Conventional imaging methods] (Ref standard)	No (% male)	Age (years): Mean/ median (range)	Primary tumour location								Histology (%)	Tumour stage (%)	Risk classification (%)
				Orbit	HN (nPM)	HN (PM)	Trunk	Extremity	GU (nBP)	GU (BP)	Other			
Baum (2011)(22) Germany	PET-CT (whole body) 5 patients received PET only. [MRI, ultrasound, contrast-enhanced CT] (clinical diagnosis inc. CT)	41 (58)	9.9[a] (1 to 20)	2	5	2	0	19	2	3	8	Alveolar 24 (59) Embryonal 17 (41)	Not reported	Group 1 0 Group 2 11 (27) Group 3 18 (44) Group 4 12 (29)
Dharmarajan (2012)(17) USA	PET-CT (coverage NR) Minority had no CT available.[CT] (NR)	94 (50)	11[b] (0.2 to 43)	5	3	34	19	21	3	9	0	Alveolar 44 (47) Embryonal 49 (52) Other 1 (1)	Stage I 10 (11) Stage II 4 (4) Stage III 48 (51) Stage IV 32 (34)	Group 1: 0 Group 2: 9 (10) Group 3: 53 (56) Group 4: 32 (34)
Eugene (2012)(16) France	PET-CT (whole body) [Bone marrow biopsy, chest radiograph, CT, MRI, bone scintigraphy] (clinical exam, histopathology, follow-up, US)	23 (70)	8.7[b] (0.75 to 21.6)	5	3	4	0	1	1	4	4	Alveolar 9 (39) Embryonal 13 (61) Other 1 (0)	Not reported	Not reported
Federico (2012) (18) USA	PET-CT (Vertex to toes) [chest CT, CT/MRI of primary and local-regional nodal basin, bone scan] (Clinical assessment, histology)	30 (57)	7.3[b] (1.3 to 23.5)	0	4	8	4	9	0	3	2	Alveolar 11 (37) Embryonal 14 (47) Other 5 (16)	Not reported	Unclear
Klem (2007)(23) USA	PET (Vertex to upper thigh, lower extremities depending on tumour location and clinical suspicion) [CT, MRI or bone scan] (Imaging, pathology, clinical findings at tumour board)	24 (42)	13[b] (1.3 to 56)	0	3	11	4	4	0	2	0	Alveolar 14 (58), Embryonal 10 (42)	Stage I 2 (8) Stage II 2 (8) Stage III 18 (75) Stage IV 5 (21)	Group 1 0 Group 2 1 (4) Group 3 18 (75) Group 4 5 (21)
Ricard (2011) (21) France	PET-CT (head to upper thigh (4 patients had scans inc legs)) [MRI , CT (primary), bone	13 (92)	9.6[b] (1.8 to 19.1)	0	4	2	0	0	0	3	4	Alveolar 10 (77), Embryonal 3 (23)	Stage I 4 (31) Stage II 1 (8) Stage III 2 (15) Stage IV 6 (46)	Not reported

	scintigraphy (metastases)] (histopathology and clinical evaluation at tumour board)													
Tateishi (2009)(19) Japan	PET-CT (head to mid-thigh (2 patients had scans inc legs)) [chest radiograph, whole body CT, MRI (primary), bone scintigraphy] (Histopathology, clinical follow-up, CSF evaluation)	35 (69)	19.8[a] (3 to 38)	1	0	18	8	8	0	0	0	Alveolar 22 (63), Embryonal 12 (34) Other 1 (3)	Stage I:Initial 3 (13) Restage 7 (70) Stage II:Initial 21 (87) Restage 3 (30)	Not reported
Volker (2007)(20) Germany	PET (whole body) [radiography (primary), chest x-ray, CT, MRI (primary and additional regions where clinically indicated), US (abdominal and additional regions where clinically indicated), bone scintigraphy] (Histopathology, clinical examination including follow-up)	46 (52) *	12.9[a] (1 to 18)*	Not reported								Not reported	Not reported	Not reported

[a]Mean [b]Median *Whole group (data not available for RMS patients only) HN head and neck nPM non-parameningeal PM parameningeal GU genitourinary nBP non-bladder/prostate BP bladder/ prostate

Table 2: Summary of patient level diagnostic data: detection of nodal and distant metastatic involvement

Study	Image	N	Sensitivity		Specificity	
			PET	conventional imaging	PET	conventional imaging
Nodal involvement						
Federico (2012)(18)	PET-CT	30	0.8	-	1	-
Ricard (2011)(26)	PET-CT	13	1	0.75	0.89	1
Tateishi (2009)(19)	PET-CT	35	1	0.86	0.95	0.9
Volker (2009)(20)	PET	4*	1	0.67	1	1
Distant metastatic involvement						
Federico (2012)(18)	PET-CT	30	1	0.17	0.92	1
Ricard (2011)(26)	PET-CT	13	1	0.83	1	0.86
Tateishi (2009)(19)	PET-CT	35	0.95	0.55	0.8	0.43

*Total N=46; 12 RMS; data available on 4 with extremity primary tumour.

Table 3: summary of detection of metastatic sites

Study	Image	N	Bone	Bone marrow	Lung	Soft tissue	Distant nodes
Federico (2012)(18)	PET-CT	30	PET-CT detected 3/4 patients. CI detected 1/4 4 other patients had some bone abnormality on PET-CT but not CI. Two of these were confirmed positives at follow-up	FI detected 2/4 patients. CI detected 0	PET-CT detected 4 nodules compared to 7 (in 6 patients) detected by CI.	PET-CT detected multiple metastatic sites in 2 patients missed by CI. Only one of these was detectable on physical examination	
Ricard (2011)(26)	PET-CT	13	All 4 patients identified by both PET-CT and CI. PET detected 8 more lesions across 3 patients		PET-CT detected 1/2 patients compared to 2/2 patients by CI.	PET-CT and CI identified 2/2 patients; PET-CT identified 4 sites compared to 3 for CI	PET-CT detected 4/4 patients compared to 3/4 for CI. PET-CT detected an additional 5 positive nodes.
Tateishi (2009)(19)	PET-CT	35	PET-CT generated 3 false positives and 1 false negative. CI generated 3 false positives and 6 false negatives			PET-CT identified 3 patients missed by CI	
Eugene (2012)(16)	PET-CT	23	PET-CT identified 3/3 patients compared to 2/3 for CI. CI also generated 1 false positive compared to 0 for PET-CT		PET-CT and CI both generated 1 false positive	PET-CT generated 1 false positive compared to 0 for CI	

FIGURE LEGENDS

Figure 1: Sensitivity and specificity of PET-CT versus conventional imaging in detection of nodal involvement plotted in ROC Space

Figure 2: Sensitivity and specificity of PET-CT versus conventional imaging in detection of distant metastatic involvement plotted in ROC Space

An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: Systematic review.

Abstract

Purpose/Objective: Rhabdomyosarcoma (RMS) management depends on risk stratification at diagnosis and treatment response. Assessment methods include CT, MRI, bone scintigraphy, histological analysis and bone marrow biopsy. Advanced functional imaging (FI) has potential to improve staging accuracy and management strategies.

Materials and Methods: We conducted a systematic review (PROSPERO 2013:CRD42013006128) of diagnostic accuracy and clinical effectiveness of FI in histologically proven paediatric RMS. PRISMA guidance was followed. We searched 10 databases to November 2013. Studies with ≥10 RMS patients which compared PET, PET-CT or DWI MRI to conventional imaging at any treatment stage were included. Study quality was assessed. Limited, heterogeneous effectiveness data required narrative synthesis, illustrated by plotting sensitivity and specificity in ROC space.

Results: Eight studies (six PET-CT, two PET) with 272 RMS patients in total were included. No DWI-MRI studies met inclusion criteria. Pooled estimates were not calculated due to sparseness of data. Limited evidence indicated initial PET-CT results were predictive of survival. PET-CT changed management of 7/40 patients. Nodal involvement PET-CT: sensitivity ranged from 80% to 100%; specificity from 89% to 100%. Distant metastatic involvement: PET-CT sensitivity ranged from 95% to 100%; specificity from 80% to100%. Data on metastases in different sites were sparse. Limited data were found on outcome prediction by PET-CT response.

Conclusions: PET/PET-CT may increase initial staging accuracy in paediatric RMS, specifically in the detection of nodal involvement and distant metastatic spread. There is a need to further assess PET-CT for this population, ideally in a representative, unbiased and transparently selected cohort of patients.

Article Summary: Strengths and limitations of this study

- This is the first systematic review of the use of advanced functional imaging in the management of rhabdomyosarcoma in children and young people.
- No studies of DWI-MRI in managing rhabdomyosarcoma of sufficient quality for inclusion were identified.
- Rigorous methodology identified the limitations of the existing research supporting this use of PET/PET-CT in the staging, prognosis development and outcome assessment of diagnosed RMS.
- Paucity of evidence prevented meta-analysis of sensitivity and specificity and contributed to considerable uncertainty around the true value of PET-CT, including whether it should be considered as an additional or a replacement diagnostic tool.
- Potential benefits of PET-CT in increasing staging accuracy were identified: specifically identification of nodal involvement and metastatic spread. Clear research recommendations for incorporation of PET-CT into future treatment trials are presented.

Background

Rhabdomyosarcoma (RMS) accounts for over 50% of sarcomas in children and young people. (1) (2) Incidence is 4.6 per million aged < 20 years. RMS frequently presents as a soft-tissue mass. The commonest sites of origin are head and neck, genitourinary tract, and limbs. Treatment is based on a multimodality approach including neoadjuvant chemotherapy, surgery where possible, radiotherapy, and adjuvant chemotherapy. Overall outcomes have improved but remain suboptimal, with three-year event-free survival (EFS) rates for patients with localised disease of around 60% in Europe and a corresponding overall survival (OS) of 80%.(3, 4) Patients who present with metastatic disease have much poorer prognoses and should be considered for novel treatment strategies. Correct staging is imperative.

Current treatment protocols rest on decisions at several points during therapy. Full initial staging employs cross-sectional imaging of the primary tumour (often with MRI); further cross-sectional imaging of the chest, abdomen, and pelvis; a radiolabelled bone scan; and pelvic bone marrow biopsies. These methods are also used to assess disease response for treatment modification and at the end of treatment as ongoing surveillance.(3) The usefulness of assessment methods is under ongoing evaluation; a recent European paediatric Soft tissue Sarcoma Group (EpSSG) analysis showed that otherwise low risk patients are unlikely to have isolated bone metastasis; in future bone scans may be omitted for these patients.(5) ~~(K. McHugh, personal communication)~~. Current assessment methods give discordant results at post-chemotherapy evaluation, highlighting the potential importance of functional imaging (FI).(6)

FI has been incorporated into management of other malignancies (e.g. staging non-small-cell lung cancer (NSCLC) and assessing treatment response in Hodgkin lymphoma) after extensive reviews found strong evidence for PET-CT.(7) It was found to be cost-effective for assessment of recurrent colorectal cancer,(8) but was less useful than non-nuclear technologies (e.g. functional MRI and nodal biopsies) in regional node evaluation in breast cancer.(9) Previous systematic reviews with meta-analysis of sarcomas generally have found uncertain and heterogeneous results.(10, 11)

This is the first systematic review of FI in children and young people with RMS diagnosis. FI has potential as an additional imaging technique or replacement for current imaging modalities for initial staging and/or response assessment.

Objective

To assess the role of FI (PET/PET-CT and DWI-MRI) in the management of RMS in childhood and adolescence and to consider its potential as a tool for improving both diagnostic (staging) and prognostic evaluation. Assessment of FI for treatment response and end of treatment evaluations were secondary aims. The review was not designed to assess the differential diagnosis of RMS in patients with suspected sarcoma.

Methods

We undertook a systematic review of the diagnostic accuracy and clinical effectiveness of PET, PET-CT and DWI MRI for assessment of histologically proven RMS in children and young people. The protocol was registered on PROSPERO (2013:CRD42013006128)(12) and PRISMA guidance adhered to. We consulted three public patient (PPI) representatives while writing the protocol and they contributed to the selection of outcomes assessed.

We searched 10 databases (including MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) from inception to November 2013 without restrictions on publication status, date or language (see appendix 1 for full list of databases and complete search strategies).

The following prespecified inclusion criteria were applied:

- **Participants**: Children and young people aged 0 to 24 years of age who are diagnosed with histologically proven RMS of any type. Studies with mixed tumour types will be included if outcome data for RMS patients are reported separately for at least one outcome. Studies with mixed populations of children/young people and adults were included where it was clear that a majority of patients were children/young people.
- **Interventions:** FI: PET +/- CT, or DWI-MRI used at any point in the management of RMS
- **Comparator:** Conventional imaging (One or more of contrast-enhanced CT or standard MRI, Technetium-99m bone scintigraphy)
- **Primary outcome:** EFS or OS at any time point.
- **Secondary outcomes:** Relapse rates, quality of life, adverse events or acceptability of the technology (by patient, carer or health professional), histological confirmation via lesional biopsy, or independent imaging or comparative classification of staging and risk classification of disease and treatment alteration in the light of imaging tests performed
- **Study design:** Prospective and retrospective studies of any design with at least 10 RMS patients for whom separate data is available for at least one outcome (following a protocol amendment due to lack of data; originally studies were required to include ≥ 20 RMS patients).

Studies were assessed for inclusion and appraised for quality by two independent reviewers. We used a tool adapted from previous ~~HTA~~ Health Technology Assessment (HTA) reviews(13, 14) for quality assessment of case series. We also assessed the reliability of the processes followed in carrying out PET and the degree to which accepted guidelines for the semi-quantification using standardised uptake values were followed ~~process~~.(15)

Data were extracted onto a prespecified form using ~~the~~ the package EPPI-Reviewer ~~software~~4 from the UK EPPI-Centre by one researcher and checked by a second (forms were piloted by two independent researchers). A third researcher was consulted where necessary. Patient-level data were extracted to enable construction of 2x2 tables for detection of nodal involvement and distant metastases. Sensitivity and specificity of PET and conventional imaging were calculated for each study and plotted in ROC space using the METANDI package in STATA. There were insufficient data to calculate pooled sensitivity and specificity.

At all stages of the review process we attempted to contact study authors about uncertain, missing or incomplete data.

Due to the limited and incomplete nature of the data reported, data at the level of individual primary, nodal or metastatic sites were summarised in a narrative synthesis. Data on survival, tumour response and treatment modification were very limited and heterogeneous so were also summarised narratively.

Results

Quantity and quality of evidence

We identified 1725 unique records and assessed 300 as full-text papers. Six studies of PET-CT(16-21) and two of PET(22, 23) were included; these were reported in a total of 15 publications(16-30) and the most up-to-date data were used in the review (see Appendix for flow diagram). All studies had a full primary English publication; in one case, survival data were available only in abstract.(29)

Seven studies included only RMS patients;(16-19, 21-23) one included a minority of RMS patients with separate data.(20) Data were reported on a total of 272 RMS patients. Two additional studies reported in abstract included >10 RMS patients but were excluded as, despite author contact, we were unable to obtain separate RMS patient data.(31, 32) One study reported separate RMS data only for the subset of patients with a primary tumour in the extremities and was included because of this data.(20) Three studies included one or more adults aged ≥25 years; these studies were included because it was clear that the great majority of patients were children/young people; median ages were 11 and 13 in two studies(17, 23) and the mean age in the third was 19.8.(19)

No studies of DWI-MRI met inclusion criteria (even after protocol amendment from >20 cases to >10 cases); only studies that assessed it for differential diagnosis with very few RMS cases were found.(33-39) These studies of DWI are discussed elsewhere. [Norman et al, Paed Radiol, in press 2014] A full list of excluded studies is available on request.

All studies used fludeoxyglucose (fluorodeoxyglucose, ~~(~~18F) as the radiopharmaceutical for PET. Most studies reported using all possible conventional imaging techniques as a comparator to PET or PET-CT (see table 2). The reference (gold) standard (as distinct from the comparison with conventional imaging) was typically a mixture of histopathology, clinical examination and follow-up.

Included studies often involved more children with unfavourable prognoses than would be expected in clinical practice: 52% of the patients in the series had an unfavourable, alveolar histology compared to 20-30% in clinical practice.(1) Histology was generally not well described and information on genetic predispositions was limited to one study which noted that no patient had a history of familial cancer syndrome. (21) Where reported, large numbers of patients had stage III or IV disease compared to around 15% with stage IV disease in clinical practice.(40) Several studies included higher numbers of patients with primary tumours of the extremities. Study characteristics are summarised in Table 1.

[table 1 about here]

All studies were opportunistic case series. Most were retrospective and did not comprise consecutive series of patients. It was often unclear how representative of the eligible population the included patients were. Details of FI procedures were often not reported. See Appendix 2 for a summary of quality assessment results. Outcome reporting was inconsistent and often incomplete. In some cases was this remedied by contacting authors.

Survival and related outcomes

Only one study (N=41) reported data on overall survival (OS).(22) This found that metabolic activity of the primary tumour on PET-CT had prognostic significance for survival (p=0.007). Also predictive of survival were PET-CT detection of nodal involvement (P=0.016), PET-CT detection of metastases

(P=0.002), and a composite outcome (PET group; P=0.002). Dichotomisation around the point SUV_{max}/SUV_{liver} = 4.6 was also predictive (P=0.002). Nodal and metastatic involvement retained statistical significance in a multivariate analysis; primary tumour intensity did not.

Three studies reported data on event-free survival (EFS).(17, 22, 29) One (N=41) found similar results for EFS as for OS, with prognostic significance for primary tumour intensity (P=0.005), lymph node detection (P=0.008), and metastases detection (P=0.01). Dichotomisation around the point SUV_{max}/SUV_{liver} = 4.6 did not predict EFS.(22) Another study (N=94) reported trends towards prognostic significance for PET-CT results dichotomised by SUV_{max} = 7.0 at initial staging (P=0.08) and by pre-RT PET-CT-positivity (after median 15 weeks chemotherapy) (P=0.06).(17) At post-RT assessment PET-CT-negative patients were significantly less likely to relapse than PET-positive individuals (P=0.02). The third study (N=38), available as an abstract, reported no prognostic significance of PET-CT at any point.(29) None of these reports demonstrated an additional prognostic value of metabolic activity indices above conventional prognostic criteria.

One study reported tumour response.(16) In a subset of 13 patients PET-CT was more likely than conventional imaging to show complete response to treatment; most of these patients were assessed by conventional imaging as having a partial response and twelve were in remission at follow-up.

Treatment alteration

PET-CT changed the management or treatment course of 7/40 patients in studies that reported this outcome.(16, 20, 21)

Quality of life and acceptability

There were no data on quality of life or acceptability of the technology. All three PPI representatives considered that additional scans (and their associated requirements of time, travel, and additional procedures) were worthwhile if they could provide additional information to inform the treatment plan and/or prognosis.

Diagnostic data

Lymph nodes

For nodal involvement, PET-CT or PET showed sensitivity of 80% (1 study)(18) or 100% (3 studies)(19-21) and specificity of 89% to 100% at the patient level. This compared to sensitivity of between 67% and 86% and specificity of 90% or 100% for conventional imaging (Table 2 and Figure 2). The ROC space 'cross-hairs' plots show each study's estimates of sensitivity and specificity as a marker at the point estimate, with 95% confidence intervals demonstrated by lines. In reading such graphs, tests with better discriminatory ability fall in the top left corner of the plot, and non-discriminatory tests fall on a 45° line between the bottom left and top right.(41)

[Table 2 about here]

[Figure 1 about here]

Nodal level data from three studies also indicated that PET-CT was able to detect more positive nodes than conventional imaging with very few false positives.(16, 18, 21) One study with fully

reported data found sensitivity and specificity of 100% for PET-CT compared to 75% and 94% for conventional imaging. (16) Where reported, PET-CT generated many fewer indeterminate results (1 versus 18/35) and more true negatives than conventional imaging .(18)

Distant metastases

For detection of distant metastatic sites, PET-CT had a sensitivity of 95% (1 study)(19) or 100% (2 studies)(18, 21) and specificity of 80% to 100% at the patient level. This compared to sensitivity of between 17% and 83% and specificity of between 43% and 100% for conventional imaging (Table 2 and Figure 2).

[Figure 2 about here]

Site level data from another study also found higher sensitivity and specificity (100% and 96%) for PET-CT compared to 66% and 91% for conventional imaging.(16)

Information on detection of metastases in different sites was extremely limited and reported at the level of individual cases (Table 3).(16, 18, 19, 21) There were indications from this very limited evidence base that PET-CT may be superior to CI for detection of bone lesions, in that both additional lesions and patients with otherwise undetectable bone involvement were identified. (16, 18, 19, 21) The number of false positives was low. PET-CT may also have potential to specifically identify marrow involvement in some patients but this finding is unclear and based on tiny numbers of patients; sensitivity appeared limited. (18) PET-CT appeared poor for detection of lung metastases.(18, 21) There were indications that PET-CT may perform better than conventional imaging in detecting soft tissue lesions in non-pulmonary locations,(18, 19) possibly including distal nodal involvement. (21)

[Table 3 about here]

Primary tumours

The ability of PET-CT to detect primary tumours was good; only one known tumour site was missed(16) and one previously occult primary was identified;(21) further details are in Appendix 3.

Discussion

We identified eight studies (272 patients) of PET or PET-CT in children and young people with RMS and no eligible studies of DWI-MRI.

The studies identified had multiple limitations. All studies were opportunistic case series open to a range of biases. As such they addressed multiple aspects of the use of PET in RMS management. Patients already had a diagnosis of RMS so the studies were not diagnostic in the conventional sense; rather they were concerned with accuracy of staging, determination of prognosis and, in some cases, evaluation of treatment outcome. The review was not designed to assess the value of PET-CT in imaging primary tumours, as the requirement for histologically proven RMS diagnosis meant that almost all patients had a known tumour site. This makes comparison to earlier reviews that included all sarcomas unhelpful.(10)

The studies included a higher proportion of more challenging cases than expected in clinical practice. Imaging methodology was not well reported. Duplicate blinded evaluation of the FI results relative

to the conventional imaging results or reference standard was often absent or unclear. Results were often not clearly or fully reported and data remained inconsistent and incomplete even after contacting authors. Our findings are therefore tentative and require confirmation by further research.

PET-CT was consistently somewhat better than conventional imaging at identifying patients with nodal involvement at initial staging and was clearly more sensitive to individual positive nodes, with fewer indeterminate results. PET-CT appeared to improve sensitivity in identification of distant metastases including identifying patients in whom distal metastatic involvement was not otherwise indicated. There is a suggestion of a role for PET-CT in detection of bone involvement but a great deal of uncertainty. Data for lung lesions are sparse and do not suggest utility. These results accord with reviews of PET-CT in staging of osteosarcoma(42) and PET in general diagnosis of pulmonary nodules.(43)

There is very limited evidence on use of PET-CT for treatment response and end of treatment evaluation. Only three studies investigated the primary outcome of survival and one evaluated tumour response. PET-CT at initial staging may have predictive value for OS and EFS. The role of PET-CT in the assessment of treatment response before and after radiotherapy is unclear. PET-CT may be superior at ascertaining complete response to chemotherapy but this is based on one small study. The tentative findings of this review suggest that the performance of PET-CT in RMS may be closer to that in Hodgkin lymphoma, NSCLC(7) and colorectal cancer(8) than in breast cancer.(9)

None of the studies reported data on the impact of FI or conventional imaging on quality of life or acceptability to any identified stakeholder group. Our PPI representatives indicated that potential additional information was highly valued and mattered more than a need for additional procedures and the resource implications of additional scans. They were particularly supportive of FI in further research with potential to clarify possible benefits of additional or alternative imaging procedures.

This systematic review represents the first thorough evaluation of the international evidence on FI in the management of childhood and adolescent RMS. Extensive searching without language restrictions ensured the inclusion of all relevant studies. We made substantial efforts to obtain supplementary data from authors. Although some studies contained patients aged >24 years we are confident from the mean/median ages reported that these were a small minority of the populations and that the relevance of the studies to the paediatric population was not significantly impacted. Excluding these studies would have resulted in the loss of data on a significant proportion of documented PET use in paediatric RMS. Studies were quality assessed and synthesised to provide an unbiased comprehensive assessment of the evidence

The key limitation was our inability to obtain all relevant data despite contacting authors. In particular we are aware of two case series in sarcoma patients which included >10 RMS patients that we could not include as authors were unable to provide separate data on RMS cases. The lack of complete patient-level data from all included studies meant we were unable to calculate pooled estimates for the sensitivity and specificity of FI and conventional imaging. However, even had we acquired full data on all known paediatric RMS patients, the total number would have remained under 300. Any answers to the review questions would have remained tentative and uncertain. There is an urgent need for more reliable disease assessment at all stages of RMS management. PET-

CT may be an option for this with sufficient prospective testing through incorporation into any future trials of RMS treatments.

Conclusion

This review highlights potential from PET-CT in imaging of children and adolescents with RMS but there is a high level of uncertainty in these data and their relevance to clinical practice. Limited evidence suggests that PET / PET-CT has potential to increase initial staging accuracy, specifically detection of nodal involvement and distant metastatic spread. There is little evidence on the impact of PET-CT in assessment of therapeutic response or post-treatment assessment. The ultimate impact of FI with PET-CT on treatment outcomes could not be addressed and it remains unclear whether and how increasing accuracy at initial staging might alter patient management and survival. It was impossible to determine whether PET-CT could replace any current imaging tests or should be used as an adjunct.

DWI-MRI has been insufficiently researched to answer questions of utility in RMS; the very limited evidence base for this is discussed elsewhere (Norman et al; Paed radiol 2014; in press).

Recommendations for further research.

- A representative, unbiased, and transparently selected cohort of patients (entering a treatment RCT) should be identified. All patients should be evaluated using PET-CT as an adjunct to conventional techniques at initial staging, treatment response, and end of treatment.
- The protocol should specify interim data analysis, potentially enabling PET-CT to replace one or more conventional staging techniques or substantially modify treatment delivery by response assessment.
- Results should be fully reported and individual patient data made available.
- Methodology of the PET-CT process should be standardised and reported fully. This should include independent reading of scans by multiple assessors blinded to conventional imaging and clinical/histological results.
- Appropriate qualitative methodologies should be used to assess the additional burden of treatment to patients and healthcare system, and resource use prospectively evaluated.
- Further comparative research on DWI-MRI in RMS is needed; researchers using this technology in RMS patients should be encouraged to publish case series in the first instance.

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Author contributions: BP Designed concept for study, wrote initial draft of protocol, supervised review, undertook analysis, reviewed and edited manuscript; GN Contributed to protocol, screened and assessed all papers, developed and conducted data extraction, wrote initial and edited later drafts of manuscript; DF: Contributed to protocol, screened and assessed all papers, developed and conducted data extraction, reviewed and edited the manuscript; KL designed and undertook the search strategy, managed the study database and reviewed and edited the manuscript; JC, MJ, SG,

DL, HM, KM contributed to the protocol, provided clinical advice to the review, reviewed and edited the manuscript.

[3670 words]

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Table 1: Participant characteristics

Study	Intervention [Conventional imaging methods] (Ref standard)	No (% male)	Age (years): Mean/ median (range)	Primary tumour location								Histology (%)	Tumour stage (%)	Risk classification (%)
				Orbit	HN (nPM)	HN (PM)	Trunk	Extremity	GU (nBP)	GU (BP)	Other			
Baum (2011)(22) Germany	PET-CT (whole body) 5 patients received PET only. [MRI, ultrasound, contrast-enhanced CT] (clinical diagnosis inc. CT)	41 (58)	9.9[a] (1 to 20)	2	5	2	0	19	2	3	8	Alveolar 24 (59) Embryonal 17 (41)	Not reported	Group 1 0 Group 2 11 (27) Group 3 18 (44) Group 4 12 (29)
Dharmarajan (2012)(17) USA	PET-CT (coverage NR) Minority had no CT available.[CT] (NR)	94 (50)	11[b] (0.2 to 43)	5	3	34	19	21	3	9	0	Alveolar 44 (47) Embryonal 49 (52) Other 1 (1)	Stage I 10 (11) Stage II 4 (4) Stage III 48 (51) Stage IV 32 (34)	Group 1: 0 Group 2: 9 (10) Group 3: 53 (56) Group 4: 32 (34)
Eugene (2012)(16) France	PET-CT (whole body) [Bone marrow biopsy, chest radiograph, CT, MRI, bone scintigraphy] (clinical exam, histopathology, follow-up, US)	23 (70)	8.7[b] (0.75 to 21.6)	5	3	4	0	1	1	4	4	Alveolar 9 (39) Embryonal 13 (61) Other 1 (0)	Not reported	Not reported
Federico (2012) (18) USA	PET-CT (Vertex to toes) [chest CT, CT/MRI of primary and local-regional nodal basin, bone scan] (Clinical assessment, histology)	30 (57)	7.3[b] (1.3 to 23.5)	0	4	8	4	9	0	3	2	Alveolar 11 (37) Embryonal 14 (47) Other 5 (16)	Not reported	Unclear
Klem (2007)(23) USA	PET (Vertex to upper thigh, lower extremities depending on tumour location and clinical suspicion) [CT, MRI or bone scan] (Imaging, pathology, clinical findings at tumour board)	24 (42)	13[b] (1.3 to 56)	0	3	11	4	4	0	2	0	Alveolar 14 (58), Embryonal 10 (42)	Stage I 2 (8) Stage II 2 (8) Stage III 18 (75) Stage IV 5 (21)	Group 1 0 Group 2 1 (4) Group 3 18 (75) Group 4 5 (21)
Ricard (2011) (21) France	PET-CT (head to upper thigh (4 patients had scans inc legs)) [MRI , CT (primary), bone	13 (92)	9.6[b] (1.8 to 19.1)	0	4	2	0	0	0	3	4	Alveolar 10 (77), Embryonal 3 (23)	Stage I 4 (31) Stage II 1 (8) Stage III 2 (15) Stage IV 6 (46)	Not reported

	scintigraphy (metastases)] (histopathology and clinical evaluation at tumour board)													
Tateishi (2009)(19) Japan	PET-CT (head to mid-thigh (2 patients had scans inc legs)) [chest radiograph, whole body CT, MRI (primary), bone scintigraphy] (Histopathology, clinical follow-up, CSF evaluation)	35 (69)	19.8[a] (3 to 38)	1	0	18	8	8	0	0	0	Alveolar 22 (63), Embryonal 12 (34) Other 1 (3)	Stage I:Initial 3 (13) Restage 7 (70) Stage II:Initial 21 (87) Restage 3 (30)	Not reported
Volker (2007)(20) Germany	PET (whole body) [radiography (primary), chest x-ray, CT, MRI (primary and additional regions where clinically indicated), US (abdominal and additional regions where clinically indicated), bone scintigraphy] (Histopathology, clinical examination including follow-up)	46 (52) *	12.9[a] (1 to 18)*	Not reported								Not reported	Not reported	Not reported

[a]Mean [b]Median *Whole group (data not available for RMS patients only) HN head and neck nPM non-parameningeal PM parameningeal GU genitourinary
nBP non-bladder/prostate BP bladder/ prostate

Table 2: Summary of patient level diagnostic data: detection of nodal and distant metastatic involvement

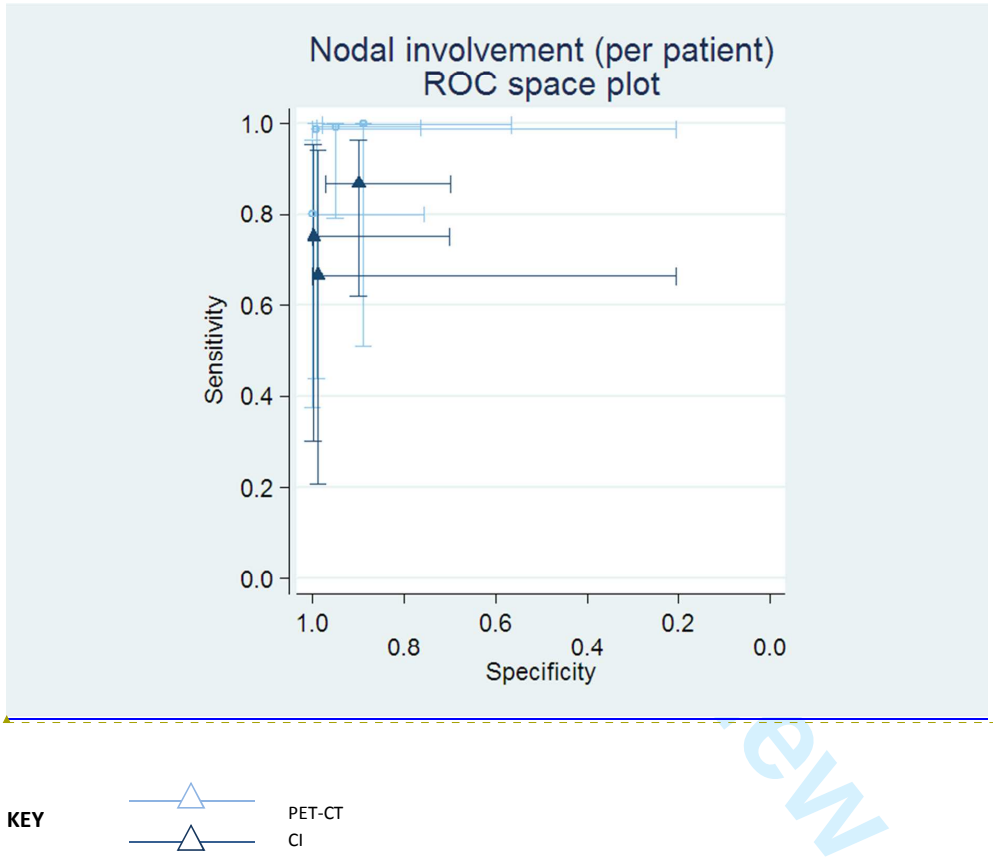
Study	Image	N	Sensitivity		Specificity	
			PET	conventional imaging	PET	conventional imaging
Nodal involvement						
Federico (2012)(18)	PET-CT	30	0.8	-	1	-
Ricard (2011)(26)	PET-CT	13	1	0.75	0.89	1
Tateishi (2009)(19)	PET-CT	35	1	0.86	0.95	0.9
Volker (2009)(20)	PET	4*	1	0.67	1	1
Distant metastatic involvement						
Federico (2012)(18)	PET-CT	30	1	0.17	0.92	1
Ricard (2011)(26)	PET-CT	13	1	0.83	1	0.86
Tateishi (2009)(19)	PET-CT	35	0.95	0.55	0.8	0.43

*Total N=46; 12 RMS; data available on 4 with extremity primary tumour.

Table 3: summary of detection of metastatic sites

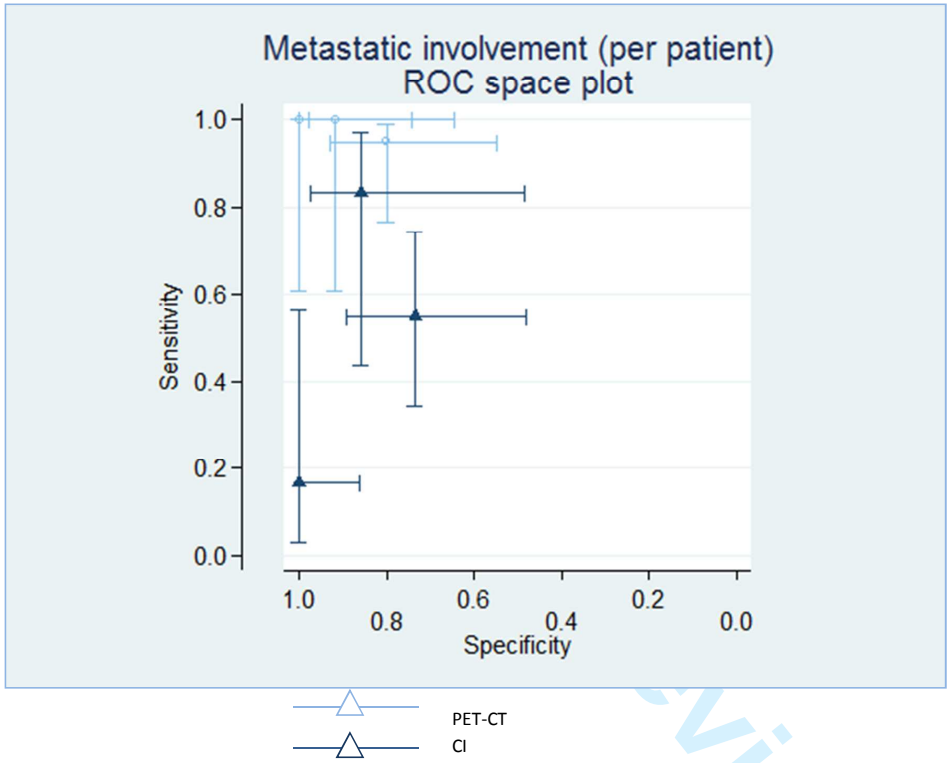
Study	Image	N	Bone	Bone marrow	Lung	Soft tissue	Distant nodes
Federico (2012)(18)	PET-CT	30	PET-CT detected 3/4 patients. CI detected 1/4	FI detected 2/4 patients. CI detected 0	PET-CT detected 4 nodules compared to 7 (in 6 patients) detected by CI.	PET-CT detected multiple metastatic sites in 2 patients missed by CI. Only one of these was detectable on physical examination	
			4 other patients had some bone abnormality on PET-CT but not CI. Two of these were confirmed positives at follow-up				
Ricard (2011)(26)	PET-CT	13	All 4 patients identified by both PET-CT and CI. PET detected 8 more lesions across 3 patients		PET-CT detected 1/2 patients compared to 2/2 patients by CI.	PET-CT and CI identified 2/2 patients; PET-CT identified 4 sites compared to 3 for CI	PET-CT detected 4/4 patients compared to 3/4 for CI. PET-CT detected an additional 5 positive nodes.
Tateishi (2009)(19)	PET-CT	35	PET-CT generated 3 false positives and 1 false negative. CI generated 3 false positives and 6 false negatives			PET-CT identified 3 patients missed by CI	
Eugene (2012)(16)	PET-CT	23	PET-CT identified 3/3 patients compared to 2/3 for CI. CI also generated 1 false positive compared to 0 for PET-CT		PET-CT and CI both generated 1 false positive	PET-CT generated 1 false positive compared to 0 for CI	

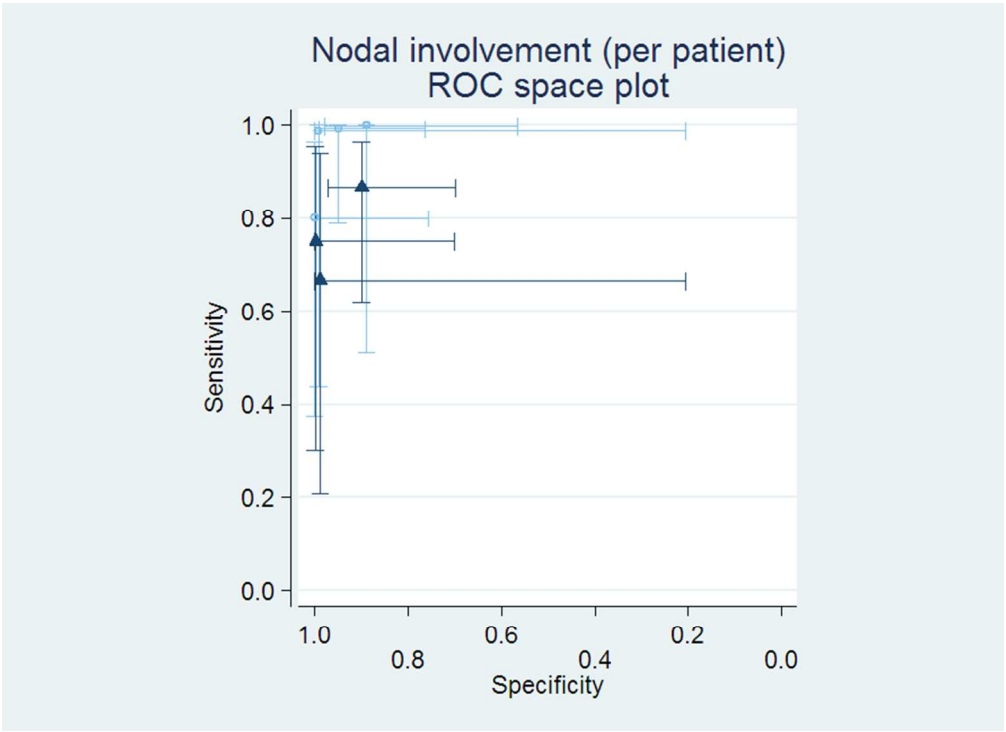
Figure 1: Sensitivity and specificity of PET-CT versus conventional imaging in detection of nodal involvement plotted in ROC Space



Formatted: Font: Bold

Figure 2: Sensitivity and specificity of PET-CT versus conventional imaging in detection of distant metastatic involvement plotted in ROC Space





75x54mm (300 x 300 DPI)

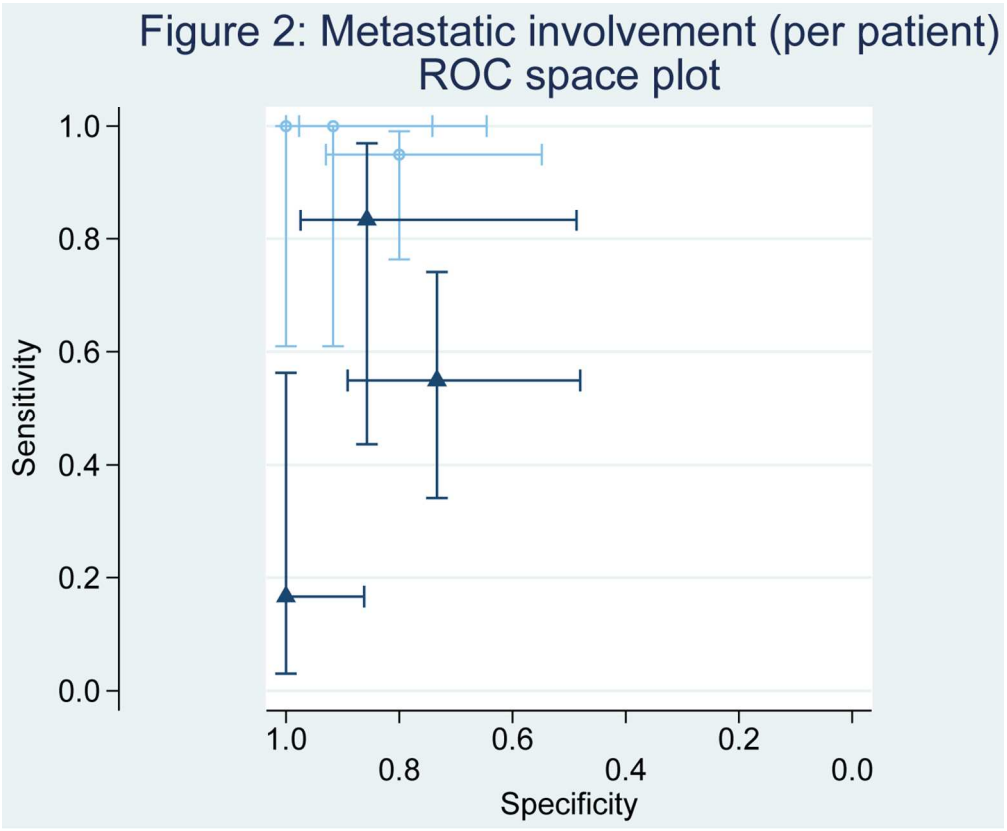


Figure 2: Metastatic involvement (per patient): ROC space plot.

Light blue denotes PET CT
Dark blue denotes conventional imaging
115x95mm (300 x 300 DPI)

Appendix 1 Searching

Databases searched for studies of FI for RMS
• MEDLINE and MEDLINE In-Process (via Ovid, 1946 to present, searched 30/October/2013); • CENTRAL (***Cochrane Central*** Register of Controlled Trials) (via Cochrane Library. CENTRAL issue 9 of 12 September 2013. Searched 30/October/2013); • Clinical Trials.gov (via http://clinicaltrials.gov/, Searched 14/November/13) • EMBASE (Excerpta Medical Database) (via OVID SP 1974 to 2013 October 29>, searched 30/October/13); • HTA database (via CRD website: http://www.crd.york.ac.uk/crdweb/HomePage.asp, searched 31/October/13) • International Cancer Research Partnership (ICRP) (via https://www.icrpartnership.org/database.cfm, searched 14/November/13) • metaRegister of Controlled Trials (mRCT) active registers (via http://www.controlled-trials.com/mrct/search.html , searched 11/November/13) • PubMed (via http://www.ncbi.nlm.nih.gov/pubmed/advanced, searched 08/November/13)
Databases searched for systematic reviews of FI for cancer
• CDSR (***Cochrane Database of Systematic Reviews***) (via Cochrane Library. CDSR issue 11 of 12 November 2013. Searched 05/November/2013) • DARE – Database of Abstracts of Reviews of Effects (via CRD website, http://www.crd.york.ac.uk/CRDWeb/. Searched 05/November/13)

Searches for studies of functional imaging for RMS:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Searched 30-10-2013

Annotated search strategy:

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1 Rhabdomyosarcoma, Alveolar/ or Rhabdomyosarcoma/ or Rhabdomyosarcoma, Embryonal/ (9170)

2 Rhabdomyosarcoma*.ti,ab. (9377)

3 1 or 2 (12196)

Line 3 captures terms for rhadomyosarcoma (RMS)

4 positron-emission tomography/ or "positron-emission tomography and computed tomography"/ (31876)

5 (photon emission adj3 tomograph*).ti,ab. (14192)

6 (positron emission adj3 tomograph*).ti,ab. (36244)

7 pet.ti,ab. (54796)

8 spect.ti,ab. (20595)

9 Fluorodeoxyglucose F18/ (18591)

10 Fluorodeoxyglucose.ti,ab. (8878)

11 (18-fdg or fdg-18 or 18f-fdg or fdg-18f).ti,ab. (5551)

12 (18fdg or fdg18 or 18ffdg or fdg18f).ti,ab. (758)

13 or/4-12 (95736)

Line 13 captures terms for Positron Emission Tomography (PET)

14 3 and 13 (112)

Line 14 combines terms for PET and RMS

15 magnetic resonance imaging/ or diffusion magnetic resonance imaging/ or diffusion tensor imaging/ (295995)

16 magnetic resonance imag*.ti,ab. (141536)

17 (MRI or MRIs).ti,ab. (142279)

18 (MR or MRs).ti,ab. (119271)

19 (diffusion adj4 (imag* or tractograph*)).ti,ab. (16385)

20 magnetic resonance tractograph*.ti,ab. (32)

21 or/15-20 (430131)

Line 13 captures terms for Magnetic Resonance Imaging (MRI)

22 21 and 3 (561)

Line 22 combines terms for MRI and RMS

23 magnetic resonance spectroscopy/ or electron spin resonance spectroscopy/ or nuclear magnetic resonance, biomolecular/ (182753)

24 spectroscop*.ti,ab. (228032)

25 nuclear magnetic resonance.ti,ab. (30681)

26 nmr*.ti,ab. (122382)

27 or/23-25 (354880)

Line 27 captures terms for spectroscopy

28 27 and 3 (49)

Line 28 combines terms for spectroscopy and RMS

29 dcemri*.ti,ab. (30)

30 functional imag*.ti,ab. (7644)

31 or/29-30 (7672)

Line 31 captures terms for functional imaging

32 31 and 3 (3)

Line 32 combines terms for functional imaging and RMS

33 14 or 22 or 28 or 32 (666)

Line 33 brings together all the records identified for the various different types of ffunctional imaging

CENTRAL (Cochrane Central* Register of Controlled Trials*) (via Cochrane Library. CENTRAL issue 9 of 12 September 2013. Searched 30/October/2013);

Search strategy:

#1 [mh ^"Rhabdomyosarcoma, Alveolar"] or [mh ^"Rhabdomyosarcoma, Embryonal"] or [mh ^Rhabdomyosarcoma] in Trials 51

#2 Rhabdomyosarcoma* in Trials 90

#3 {or #1-#2} 90

Clinical Trials.gov (via http://clinicaltrials.gov/, **Searched 14/November/13)**

Search strategy:

rhabdomyosarcoma* and (tomograph* OR PET* OR SPECT* OR “magnetic resonance*” OR MRI OR MRIs OR spectroscop* or “functional imag* or Fluorodeoxyglucose” OR dcemri*) – 10 records

EMBASE (*Excerpta Medical Database*) (via OVID SP 1974* to 2013 October 29*>, searched 30/October/13)

Search Strategy:

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1 rhabdomyosarcoma/ or embryonal rhabdomyosarcoma/ (13925)

2 Rhabdomyosarcoma*.ti,ab. (11270)

3 or/1-2 (16101)

4 positron emission tomography/ (80086)

5 computer assisted emission tomography/ (16482)

6 (photon emission adj3 tomograph*).ti,ab. (16812)

7 (positron emission adj3 tomograph*).ti,ab. (44186)

8 pet.ti,ab. (80248)

9 spect.ti,ab. (29923)

10 Fluorodeoxyglucose F18/ (33010)

11 Fluorodeoxyglucose.ti,ab. (11286)

12 (18-fdg or fdg-18 or 18f-fdg or fdg-18f).ti,ab. (11612)

13 (18fdg or fdg18 or 18ffdg or fdg18f).ti,ab. (1984)

14 or/4-13 (156421)

15 14 and 3 (309)

16 nuclear magnetic resonance imaging/ or diffusion tensor imaging/ or diffusion weighted imaging/ (459617)

17 magnetic resonance imag*.ti,ab. (161366)

18 (MRI or MRIs).ti,ab. (199744)

19 (MR or MRs).ti,ab. (131475)

20 (diffusion adj4 (imag* or tractograph*)).ti,ab. (20139)

21 magnetic resonance tractograph*.ti,ab. (36)

22 or/16-21 (571190)

23 22 and 3 (1229)

24 nuclear magnetic resonance spectroscopy/ (98107)

25 electron spin resonance/ (32873)

26 spectroscop*.ti,ab. (232789)

27 nuclear magnetic resonance.ti,ab. (32396)

28 nmr*.ti,ab. (141440)

29 or/24-28 (386947)

30 3 and 29 (71)

31 dcemri*.ti,ab. (80)

32 functional imag*.ti,ab. (9444)

33 or/31-32 (9518)

34 33 and 3 (8)

35 15 or 23 or 30 or 34 (1432)

HTA database (via CRD website: http://www.crd.york.ac.uk/crdweb/HomePage.asp, searched 31/October/13)

Search strategy:

1) MeSH DESCRIPTOR Rhabdomyosarcoma EXPLODE ALL TREES IN HTA 0 hits

2) ((rhabdomyosarcoma*)) and (Project record:ZDT OR Full publication record:ZDT)1 hit

3) #1 OR #2 1 HIT

International Cancer Research Partnership (ICRP) (via https://www.icrpartnership.org/database.cfm, searched 14/November/13)

Search strategy:

Containing All of These Words: Rhabdomyosarcoma*
Funding Years: 2013, 2012, 2011, 2010, 2009, 2008, 2007, 2006, 2005, 2004, 2003, 2002, 2001, 2000
CSO Codes:

- 4.1 - Technology Development and/or Marker Discovery
- 4.2 - Technology and/or Marker Evaluation with Respect to Fundamental Parameters of Method
- 4.3 - Technology and/or Marker Testing in a Clinical Setting
- 4.4 - Resources and Infrastructure Related to Early Detection, Diagnosis or Prognosis

17 hits

metaRegister of Controlled Trials (mRCT) active regsiters (via http://www.controlled-trials.com/mrct/search.html **, searched 11/November/13)**

Search strategy:

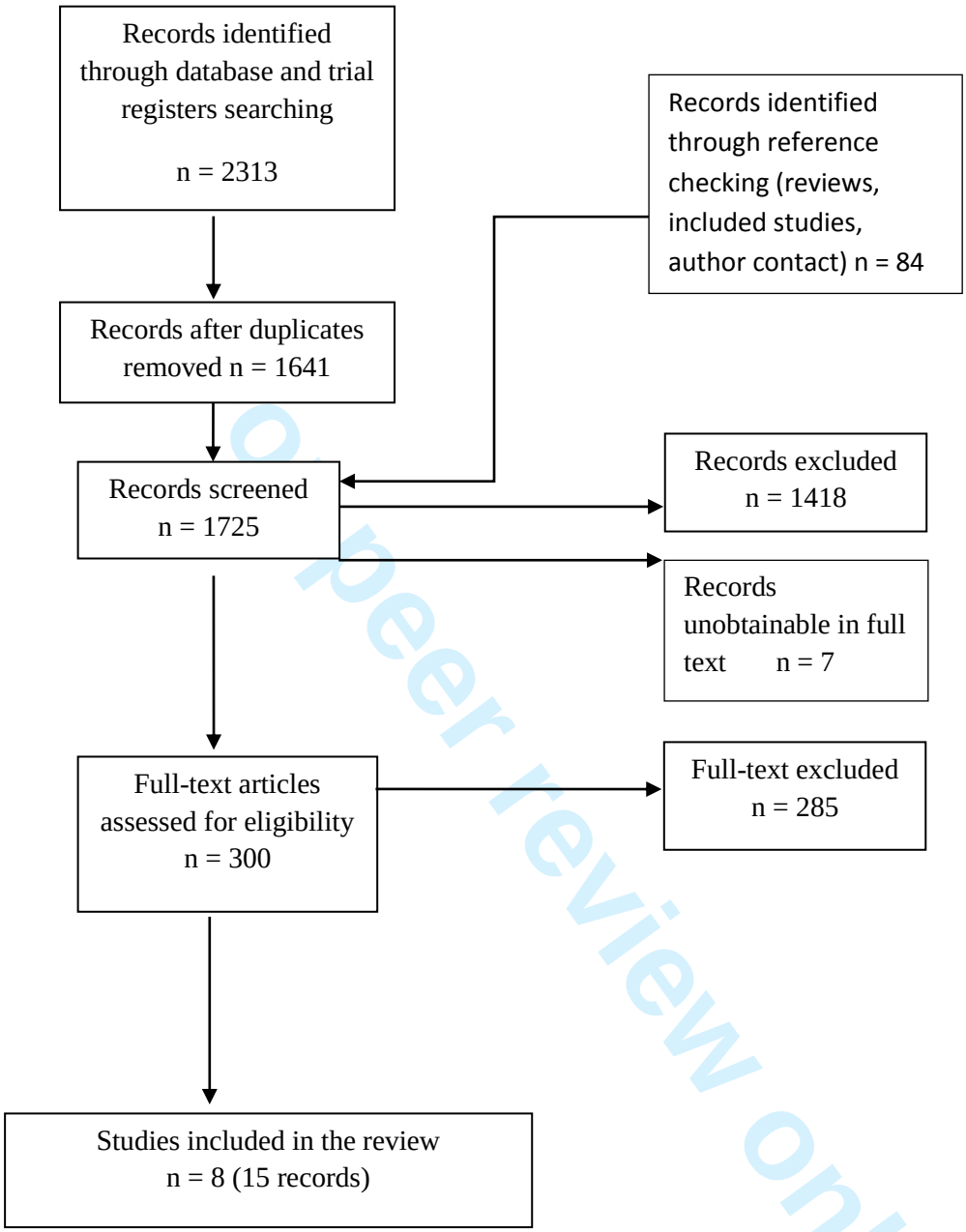
Rhabdomyosarcoma* in all databases 46 hits

PubMed (via** http://www.ncbi.nlm.nih.gov/pubmed/advanced**, searched 08/11/13)

Search strategy:

#1	Search rhabdomyosarcoma[MeSH Terms]	8930
#2	Search Rhabdomyosarcoma, Alveolar[MeSH Terms]	558
#3	Search Rhabdomyosarcoma, Embryonal[MeSH Terms]	702
#4	Search Rhabdomyosarcoma*[Title/Abstract]	9174
#5	Search (#1 or #2 or #3 or #4)	11962
#9	Search "Positron-Emission Tomography"[Mesh] OR "Positron-Emission Tomography and Computed Tomography"[Mesh]	28349
#10	Search ("photon emission" AND tomograph*[Title/Abstract])	14403
#11	Search (positron emission AND tomograph*[Title/Abstract])	36210
#12	Search pet[Title/Abstract]	53207
#13	Search spect[Title/Abstract]	20474
#15	Search "Fluorodeoxyglucose F18"[Mesh]	17448
#16	Search Fluorodeoxyglucose[Title/Abstract]	8566
#20	Search ("18-fdg" or "fdg-18" or "18f-fdg" or "fdg-18f"[Title/Abstract])	5387
#22	Search ("18fdg" or "fdg18" or "18ffdg" or "fdg18f"[Title/Abstract])	702
#30	Search magnetic resonance imag*[Title/Abstract]	134446
#31	Search (MRI or MRIs[Title/Abstract])	371243
#32	Search (MR or MRs[Title/Abstract])	120807
#35	Search ((diffusion AND imag*) or (diffusion AND tractograph*)[Title/Abstract])	0
#36	Search magnetic resonance tractograph*[Title/Abstract]	28
#37	Search ("magnetic resonance spectroscopy"[Mesh] OR "nuclear magnetic resonance, biomolecular"[Mesh] OR "electron spin resonance spectroscopy"[Mesh] OR "nuclear magnetic resonance, biomolecular"[Mesh])	172389
#38	Search spectroscop*[Title/Abstract]	225674
#39	Search nuclear magnetic resonance[Title/Abstract]	29424
#40	Search nmr*[Title/Abstract]	118295
#41	Search dcemri*[Title/Abstract]	26
#42	Search functional imag*[Title/Abstract]	6839
#43	Search ((#9 or #10 or #11 or #12 or #13 or #15 or #16 or #20 or #22 or #30 or #31 or #32 or #36 or #37 or #38 or #39 or #40 or #41 or #42))	848762
#44	Search (#5 and #43)	663

Figure 1 Flow of studies through the review



Appendix 2: Quality assessment

Study Assessment tool

Possible answers for each criterion were "yes", "no", and where relevant, "unclear", or "not applicable".

- Were the selection/eligibility criteria adequately reported?
- Is the sample likely to be representative?
- Were patients recruited prospectively?
- Were patients recruited consecutively?
- Was the participation rate adequate (>80% of those eligible)
- Was there at least 80% follow-up from baseline?
- Was loss to follow-up reported?
- Were relevant prognostic factors reported? (e.g. histology, location of primary tumour)
- Were other relevant confounding factors reported? (e.g. excisional biopsy, variations in timing of imaging including variations in treatment point when imaging took place)
- Was an appropriate measure of variability reported?
- Was there an appropriate statistical analysis?
- Were there any other important limitations?
- Were the FI results assessed blind to the reference standard?
- Were the FI results assessed blind to the results of CI?
- Were there two independent assessors?

Intervention assessment criteria

Possible answers for each criterion were "yes", "no", and where relevant, "unclear", or "not applicable".

- Was the same scanner used for baseline and follow-up?
- Was residual activity in the syringe and injection tubing measured to accurately determine administered dose?
- Was an appropriate uptake time used (baseline minimum 60 minutes; baseline ± 10 minutes at follow-up)?
- Were acquisition technique and reconstruction parameters maintained for baseline and follow up; was the same CT protocol used?
- Were serum glucose and average liver SUV recorded before each PET?
- Were all patients weighed before imaging, at facility, using calibrated scale?
- Were dose calibrators calibration maintained and dose calibrator clocks synchronised with scanner clocks?
- Were screensaves or other documentation used to improve reproducibility in defining regions of interest between baseline and follow-up?

Results of study quality assessment

Study	Selection criteria	Representative sample	Prospective recruitment?	Consecutive recruitment?	Adequate participation?	Adequate retention?	Loss to follow up?	Prognostic factors reported?	Confounding factors reported?	Appropriate measures of variability?	Appropriate statistical	standard	Blind to CI	Two assessors?
Baum (2011)[36]	yes	unclear	no	unclear	unclear	yes	yes	yes	yes	yes	yes	no	unclear	yes
Dharmarajan (2012)[46]	yes	unclear	no	unclear	unclear	yes	yes	yes	yes	yes	yes	unclear	unclear	unclear
Eugene (2012)[38]	yes	yes	unclear	yes	yes	no	yes	yes	yes	yes	yes	unclear	yes	yes
Federico (2012)[40]	yes	yes	no	unclear	unclear	NA	NA	yes	yes	yes	yes	yes	yes	no
Klem (2007)[43]	yes	unclear	no	no	yes	yes	unclear	yes	no	no	no*	unclear	unclear	unclear
Ricard (2011)[15]	yes	Yes ^	no	unclear	unclear	yes	yes	yes	yes	no	no	unclear	yes	yes
Tateishi (2009)[16]	yes	unclear	no	unclear	unclear	yes	yes	yes	yes	yes	yes	yes	yes	yes
Volker (2007)[35]	yes	unclear	yes	unclear	unclear	NA	NA	no	yes	yes	yes	yes	yes	yes

*Those who had had chemotherapy and those who had not were analysed together. ^ but note atypical histology/gender balance

Intervention quality

Study	Same scanner used?	Administered dose accuracy?	Uptake time appropriate?	Acquisition technique/reconstruction parameters maintained?	Serum glucose and average liver SUV	Patient weighed	Adequate calibration	Reproducibility of ROI
Baum (2011)[36]	NA	unclear	yes	NA	yes	unclear	unclear	unclear
Dharmarajan (2012)[46]	unclear	unclear	unclear	unclear	unclear	unclear	unclear	unclear
Eugene (2012)[38]	unclear	unclear	yes	yes	unclear	unclear	unclear	Unclear*
Federico (2012)[40]	NA	unclear	yes	NA	unclear	unclear	unclear	unclear
Klem (2007)[43]	NA	unclear	No‡	NA	unclear	unclear	unclear	unclear
Ricard (2011)[15]	unclear	unclear	yes	unclear	unclear	unclear	unclear	unclear
Tateishi (2009)[16]	NA	unclear	yes	NA	unclear	unclear	unclear	unclear
Volker (2007)[35]	NA	unclear	unclear	unclear	unclear	unclear	unclear	unclear

**Blood glucose level was controlled but it is unclear if average liver SUV was recorded before each PET.‡45 to 60 minutes*

Appendix 3: Results of imaging of primary tumours

Study	Image	N	Primary tumour imaging details	SUV_{max}: mean (range)
Baum (2011)[36]	PET-CT	41		CRG2: 3.7 (SD 1.9)(N =11) CRG3: 3.6 (SD 2.3) (N = 18) CRG 4: 5.2 (SD 3.2) (N = 12)*
Dharmarajan (2012)[46]	PET-CT	94		7.0 (median) (0 to 31)(N =58)
Eugene (2012)[38]	PET-CT	23	PET detected 17/18 tumours; CI detected 18/18; (4 sites were completely excised before imaging, 1 was not clearly identified at diagnosis)	6.2(median) (2.7-15.4)
Federico (2012)[40]	PET-CT	30	PET detected all 21 tumours (8 completely excised before imaging; 1 unknown primary)	7.2 (2.5 to 19.2) (N = 18)
Klem (2007)[43]	PET	24	23 tumours evaluated (1 previously completely excised)	Initial staging: 7.7 (4.1 to 12.7) 1-13 days post-chemotherapy (first dose): 4.7 (2.4 to 8.4)
Ricard (2011)[15]	PET-CT	13	PET-CT detected 11/11 tumours including previously occult primary; CI detected 10/11. 2 patients had prior surgery; both PET and CI missed 1 microscopic residual lesion. Follow-up (N = 8) PET and CI both detected 3 residual local disease cases and 4 clear results. PET clear for 1 patient with positive CI; PET result confirmed true negative by follow-up.	Initial staging: 3.7 (median) (2 to 6.9) Follow-up (N = 8) 5.8 (median) (5.2-6.1)
Tateishi (2009)[16]	PET-CT	35	Both PET-CT (using CT component) and CI correctly classified the T stage in all patients	NR
Volker (2007)[35]	PET	46 (11 RMS)	Both PET and CI detected all primary tumours	7.0 (SD 3.4)

CRG clinical risk group; SD standard deviation *all figures are mean SUV_{max}/SUV_{liver}

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2, Table 1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	1,2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Table 1 P3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	P3, Appendix
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	P2, Fig 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	P3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	P3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	P3, Appendix
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	P3

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	P3

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	P4, appendix
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	P3, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	P4-6, Figs 2+3, tables 3-4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A but see figs 2+3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	P6-7
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	P6-7
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	P6-8
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	P8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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