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Utility of positron emission tomography/computed tomography (PET/CT) imaging in the evaluation of sarcomas: A systematic review

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ABSTRACT

Background: Sarcomas are a heterogeneous group of malignant tumours with variable clinical outcomes. Their presence in multiple body locations represents significant diagnostic and therapeutic challenges. Positron emission tomography/computed tomography (PET/CT) is an imaging tool that provides semiquantitative measurements of radiotracer concentration in tissue, such as SUV_{max} (standardised uptake value) and is increasingly used in clinical practice. This systematic review aims to evaluate the utility of PET/CT in sarcoma grading and prognostication, evaluation of treatment response, staging and restaging.

Methods: Relevant studies published from January 2003 to August 2017 evaluating the utility of PET/CT in sarcoma grading and prognostication, staging, evaluation of treatment response and restaging were systematically searched for in scientific databases (*e.g.* PubMed, Medline and Embase) using key terms, including “soft tissue sarcoma,” “osteosarcoma,” “utility” and “PET/CT”. Additionally, references of identified studies were reviewed. Study quality was assessed by “Quality Assessment of Diagnostic Accuracy Studies”.

Results: A total of 12 prospective studies (level II to III evidence) were included in the review for tumour grading and prognostication. There was a strong correlation between SUV and tumour grade where majority of intermediate/ high-grade STS have a significantly higher SUV_{max}. PET/CT has also shown potential in prognostication where decrease in SUV_{max} correlated with recurrence-free survival in both osteosarcoma and STS. Furthermore, 8 prospective trials of level II to IV evidence according to Oxford Centre of Evidence-based Medicine (CEBM) demonstrated the use of PET/CT in early identification of patients who will respond to treatment where ≥60% decrease in FDG uptake resulted in sensitivity and specificity of 100% and 71% respectively for assessment of histopathologic response. 11 retrospective trials (level III to IV evidence) reported on the use of PET/CT in staging and restaging with heterogeneous results.

Conclusion: Overall, higher quality evidence demonstrated PET/CT to be an important contributor towards sarcoma grading, prognostication and evaluation of treatment response. Larger prospective trials will be helpful to further establish the clinical value of PET/CT in sarcoma staging and restaging.

1. Introduction

Sarcomas are a histologically heterogeneous group of malignant tumours with highly variable characteristics and clinical outcomes (Burningham et al., 2012). They are uncommon tumours of mesenchymal origin accounting for 0.7% of adult malignancies (Martin Broto et al., 2017). Their locations in almost all body locations present unique challenges for diagnosis and management where 75% of soft tissue sarcomas (STS) are found in the extremities, with 10% in the thoracic wall and another 10% in the retroperitoneum (Mastrangelo et al., 2012). These challenges have presented opportunities for evaluation and validation of new imaging techniques. In particular, fluorine-18-fluorodeoxyglucose positron emission tomography combined with computed tomography (FDG-PET/CT) has increasingly been used for diagnosis and treatment evaluation of patients with STS (Ell, 2006; Mastrangelo et al., 2010). PET/CT imaging generates high-resolution three-dimensional images and utilises radiotracers specific for biologic processes (Choi et al., 2016). In particular, fluorine-18 fluorodeoxyglucose (FDG) is the most commonly used imaging agent in cancer imaging to report regional tissue metabolism (Zhu et al., 2011). As the positron radiolabel has such high imaging energies, semiquantitative measurements of radiotracer concentration in tissue can be made, such as SUV_{max} (McCarville et al., 2005). Subsequently, FDG-PET can determine the tumour characteristics of high metabolism and an increased rate of glucose utilisation compared with normal tissues (Schuetze, 2006). The high capacity of glucose utilisation is a possible reflection of

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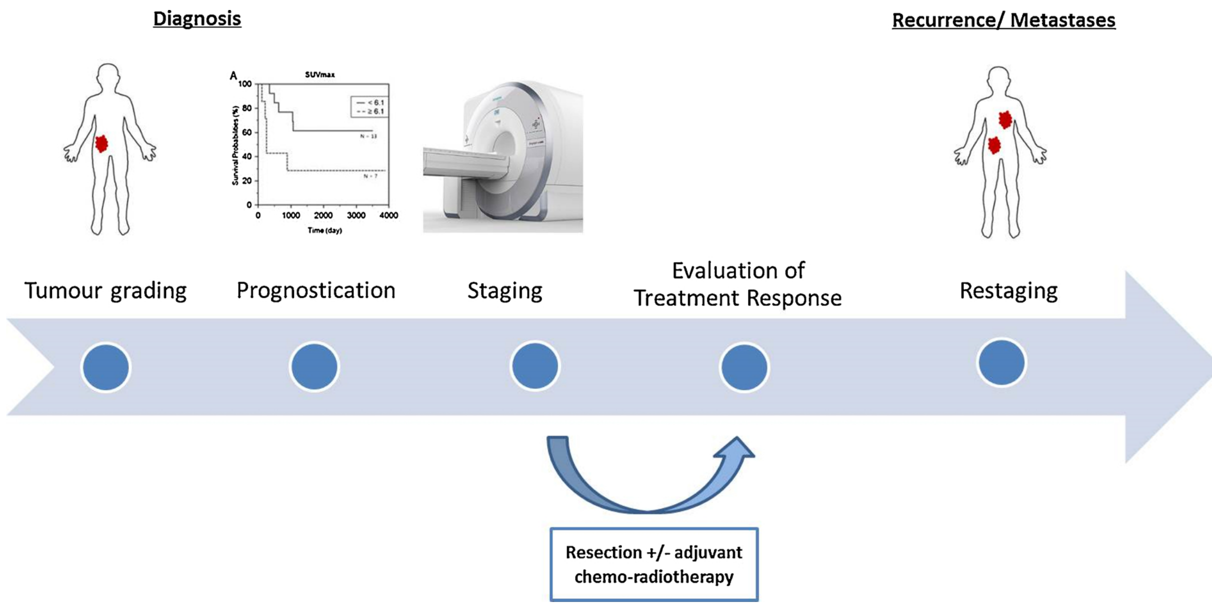

Fig. 1. Overview of sarcoma progression. The utility of PET/CT imaging is discussed in the various aspects of sarcoma progression, namely 1) tumour grading, 2) prognostication, 3) staging, 4) monitoring of treatment response and 5) restaging of patients with sarcomas.

the malignant nature of a tumour (Lee et al., 2012). This important characteristic is the basis for determination of tumour grade, quantitation of changes in response to treatment, and prognostication that are made with FDG-PET/CT imaging (Mody et al., 2010; Park et al., 2008). Furthermore, treatment of malignant sarcomas in the last decade has emphasised the need for pre-operative neoadjuvant chemotherapy for high-grade tumours (Brenner et al., 2006; Kumar et al., 2006). As such, PET/CT has potentially wide-ranging utility in sarcomas. However, the role of this imaging technique is not clearly defined in guidelines or consensus protocols. There have been up to 8 literature reviews which discuss the usefulness in PET/CT imaging in sarcoma (Ioannidis and Lau, 2003; Muheremu et al., 2017; Rodríguez-Alfonso et al., 2014; Toner and Hicks, 2008; Gabriel and Rubello, 2016; Kandathil and Subramaniam, 2019; Norman et al., 2015; Kassem et al., 2017). Nonetheless, these reviews discuss the utility of PET/CT imaging either in specific sarcoma subtypes or focus on a single aspect of PET/CT in the management of sarcoma (Fig. 1).

We aim to provide a comprehensive overview of the utility of FDG-PET/CT in the assessment of sarcomas in the following areas, namely 1) tumour grading, 2) prognostication, 3) evaluation of treatment response, 4) staging and 5) restaging of patients with sarcomas.

2. Methods

2.1. Literature search

A literature search was performed for relevant studies published from January 2003 to August 2017 evaluating the utility of PET/CT in sarcoma grading and prognostication, staging, evaluation of treatment response and restaging. Articles were systematically searched for in scientific databases, including PubMed/ Medline, Embase, Scopus and Cochrane Library using key terms, including “soft tissue sarcoma,” “osteosarcoma,” “utility” and “PET/CT”. Reference lists of identified studies and relevant reviews were screened to identify eligible additional studies. Editorials or letters, conference proceedings, case reports, pre-clinical studies and animal studies were excluded from this review. Only full-text articles written in English were included in our systematic review. The title and abstracts were reviewed according to the established selection criteria and rejected when ineligible. The remaining publications were subjected to full-text review to determine eligibility. For studies whose eligibility for the inclusion criteria failed to reach consensus between the two authors, a third author was present to settle the disputes.

2.2. Study quality assessment

Two authors independently assessed the quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. QUADAS is a system composed of 14 items including the patient spectrum covered, reference standards, test execution, study withdrawals, indeterminate results as well as verification, review, clinical review, incorporation, and disease progression biases. A 1-point score was given for each item and studies with high scores were considered as good reports. Each study was scored as ‘+’ (positive), ‘-’ (negative) or ‘U’ (unclear). In case of disagreement, a third author made the final decision. Studies with < 7 ‘+’ were considered to be of low methodological quality and with a high risk of bias. In case of discrepancies in quality assessment between the two authors, a consensus was reached through discussion.

Of the 187 articles screened, 34 were selected for the final review. 52 articles were removed due to search duplication. Based upon title and abstract reading, 78 articles were not relevant to the topic leading to the full-text screening of 57 articles where 34 articles were included in our review. A flow chart of the selection of studies for the systematic review is shown in Fig. 2. Majority of the studies were of relatively high quality according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool (Supplementary Table 1).

3. Results

In total, 34 studies met our inclusion criteria and were described in this review. Higher quality evidence was available for the use of PET/CT imaging in tumour grading, prognostication and monitoring of tumour response compared to staging and restaging. 12 prospective studies of level II to III evidence were included for the review of tumour grading and prognostication. Furthermore, 8 prospective and 2 retrospective trials of level II to IV evidence demonstrated the use of PET/CT in early identification of patients who will respond to treatment. In contrast, 11 retrospective trials of level III to IV evidence discussed the use of PET/CT in staging and restaging. The results of the included studies evaluating the utility of PET/CT imaging in sarcoma have been summarised in Tables 1–3.

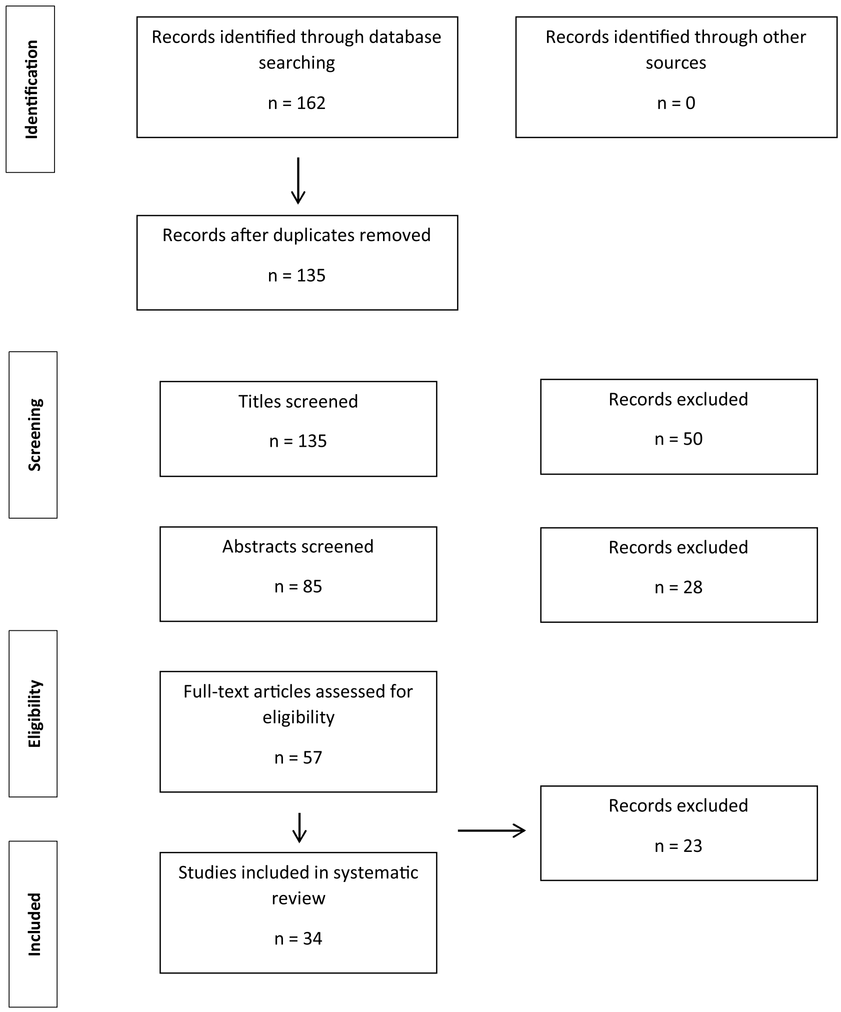

Fig. 2. Flowchart for selection of studies included in the systematic review.

In regard to the utility of PET/CT in tumour grading of sarcoma, studies have shown significant correlation between SUV_{max} and tumour grading and the discriminative ability of tumour SUV to differentiate low-grade from high-grade sarcomas in suitable subtypes. However, there may be limited usefulness in differentiating between low-grade sarcomas and benign tumours. In addition, in STS, ≥60% decrease in FDG uptake resulted in sensitivity and specificity of 100% and 71% respectively for assessment of histopathologic response. Similarly, in osseous sarcoma, ≥60% decrease in FDG uptake resulted in sensitivity and specificity of 75% and 88% respectively for assessment of metabolic responders. For the staging of sarcomas, PET/CT imaging may be more useful for staging of sarcomas with a higher probability of metastases as it increases the yield of staging by limiting its use to patients who are either at greater risk of systemic disease or expected to have a higher proportion of extrathoracic metastases. For the restaging of sarcomas, although there was superior sensitivity and specificity in detection of local recurrence compared to conventional imaging, these studies were largely retrospective in nature and of lower quality evidence.

4. Discussion

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) is an imaging tool that measures a tumour's metabolic activity and is increasingly used in clinical practice (Burningham et al., 2012). Metabolic data acquired by FDG-PET/CT, including SUV_{max} and total lesion glycolysis (TLG), may facilitate accurate grading and prognostication in sarcomas where glycolytic metabolic activity of high-grade tumours is higher than that of low-grade or benign tumours (Rodríguez-Alfonso et al., 2014). The standardised uptake value (SUV) measured by FDG-PET/CT is defined as the ratio of activity per unit volume of a region of interest to the activity per unit whole body volume and is considered to be a semi-quantitative parameter, with the maximal standardised uptake value (SUV_{max}) representing the highest metabolically active region in the tumour (Toner and Hicks, 2008). Notably, studies have shown a strong correlation between standardised uptake value (SUV) and tumour grade where a higher SUV_{max} has been found to correlate with both tumour grade and tumour greatest dimension (Benz et al., 2010a; Fendler et al., 2015; Tateishi et al., 2006). This allows PET/CT to accurately distinguish between different histologic grades and a correlation coefficient of up to 0.94 has been demonstrated (Tateishi et al., 2006). In addition, other studies have used the average lesion SUV (SUV_{mean}) to discriminate between low- and high-grade sarcomas (Charest et al., 2009; Rakheja et al., 2012). Given the strong statistical correlation between SUV and tumour grading, metabolic data from PET/CT may act as a surrogate marker for tumour grade (Rakheja et al., 2012). This would be clinically beneficial as consideration of neoadjuvant treatment may be more warranted in the presence of confirmation of a high-grade tumour. PET/CT has also shown potential in prognostication where decrease in SUV_{max} correlated with recurrence-free survival (Table 1). As FDG-uptake has been shown to be correlated with tumour grade, mitotic rate and cellularity, additional studies have also evaluated the ability of this technique to predict patient outcomes (Schwarzbach et al., 2005;

Table 1
Utility of PET/CT in prognostication of sarcomas.

Author(s)	Type of Study	No. of Patients	Histology	Grade	Location	SUV_{max} cut-off	Conclusion
Charest M, Hickeson M, Lisbona et al. (Charest et al., 2009)	Retrospective	212	Leiomyosarcoma Ewing's sarcoma Liposarcoma Synovial sarcoma Malignant peripheral nerve sheath tumour Malignant fibrohistiocytic tumours	Grade 2 or 3	Extremity (151) Trunk (61)	$SUV_{max} \geq 2.5$	94% for the discrimination of low-grade and high-grade sarcomas
Schwarzbach MH, Hinz U, Dimitrakopoulou-Strauss A, et al. (Schwarzbach et al., 2005)	Retrospective	74	Liposarcoma (39) MFH (11) Leiomyosarcoma (8)	85.2 grade 2 or 3 (FNCLCC)	Extremity – (57%) Retroperitoneum – (31%)	Pre-treatment < 1.59 1.59 to 3.6 ≥ 3.60	5 year survival 66% 45% 38% Higher SUV correlated with higher grade
Herrmann K, Benz MR, Czernin J, et al. (Herrmann et al., 2012)	Retrospective	39	NOS (17) Synovial (3) Myxofibrosarcoma (6) Liposarcoma (5) Leiomyosarcoma (3) MPNST (1) Other (4)	All grade 2 or 3	Extremity – 31 Retroperitoneum/ Abdominal – 3 Chest/ Trunk - 5	≥ 26.0	Optimal cut-off values for early and late decreases in $SUV_{max}$of 26% and 57% respectively were significant predictors of survival
Fuglø HM, Jørgensen SM, Loft A, et al. (Fuglo et al., 2012)	Retrospective	89	STS (59) Osteosarcoma (30)	All grade 2 or 3	STS Femur (19) Foot/ Below knee (11) Pelvis (8) Thorax/ Scapula (6) Antebrachium/ Wrist (6) Shoulder/ Humerus (5) Knee joint (3) Unknown primary tumour (1) Osteosarcoma Femur (10) Pelvis (6) Tibia or fibula (5) Scapula (2) Humerus (2) Ulna (2) Hip or thoracic spine (3)	≤ 10	5-year survival was 81 % among patients with $SUV_{max} \leq 10$), 33 % for those with $SUV_{max} > 10$
Rakheja R, Makis W, Tulbah R, et al. (Rakheja et al., 2013)	Prospective	66	Liposarcoma (13) Osteosarcoma (10) Undifferentiated (9) Ewing sarcoma (7) Leiomyosarcoma (8) Synovial (5) Fibrosarcoma (5) Chondrosarcoma (6) Other (3)	Low (13) Intermediate(16) High (37)	Upper extremity (19) Lower extremity (47)	Presence of necrosis	Presence of necrosis and the volume of necrosis, as identified on the staging FDG PET/CT and after adjusting for SUV_{max}, are strong independent adverse prognostic factors for disease recurrence and death

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Table 1 (*continued*)

Author(s)	Type of Study	No. of Patients	Histology	Grade	Location	SUV_{max} cut-off	Conclusion
Hoshi M, Oebisu N, Takada J, et al. (Hoshi et al., 2014)	Retrospective	243	Myxoid liposarcoma (22) Pleomorphic liposarcoma (21) Leiomyosarcoma (7) Well-differentiated liposarcoma (6) Malignant peripheral nerve sheath tumour (5) Synovial sarcoma (4) Epithelioid sarcoma (4) Liposarcoma (3) Gastrointestinal mesenchymal tumour (3) Pleomorphic malignant fibrous histiocytoma (3) Myofibroblastic sarcoma (2) Myxofibrosarcoma (2) Solitary fibrous tumour (2) Alveolar soft part sarcoma (1) Clear cell sarcoma (1)	Unknown	Unknown	Tumour ≥5 cm in size and SUV_{max} ≥2.0	Tumours measuring ≥5 cm size and SUV_{max} ≥2.0 associated with a worse survival rate SUV_{max} of distant metastases and local recurrences were identified to be significantly affected by tumour size
Choi ES, Ha SG, Kim HS, et al. (Choi et al., 2013)	Retrospective	66	Rhabdomyosarcoma (14) PNET/Ewing sarcoma (8) Synovial (7) Liposarcoma (5) Malignant fibrous histiocytoma (5) Angiosarcoma (4) Fibrosarcoma (3) Leiomyosarcoma (3) Clear cell sarcoma of soft tissue (1) Extraskeletal chrondrosarcoma (1) Undifferentiated (4)	Grade 1 (3) Grade 2 (12) Grade 3 (40)	Head and neck (7) Thorax (9) Abdominopelvic cavity (15) Upper extremity (6) Lower extremity (18)	TLG ≥250, SUV_{max} ≥6.0, and MTV ≥ 40 cm^3	TLG exhibited greater accuracy than SUV_{max} or MTV in ROC analysis for survival (area under curve, AUC, 0.802, 0.726 and 0.681, respectively)
Skamene SR, Rakheja R, Dahlstrom KR, et al. (Skamene et al., 2014)	Prospective	120	Soft-tissue sarcoma (82) Osteosarcoma (32) Cartilage (6)	Unknown	Limb and girdle	SUVmax ≥10.3	SUV(max) < 10.3 had better DFS and OS compared with patients with SUV(max) ≥10.3 SUV_{max} ≥10.3 correlated with twofold risk of progression and 2.4 times greater risk of death
Andersen KF, Fuglo HM, Rasmussen SH, et al. (Andersen et al., 2015a)	Retrospective	92	STS (55) Osteosarcoma (37)	High-grade	Upper extremity (16) Lower extremity (58) Trunk (26)	SUV_{max}	Accuracy of SUV_{max} and tumour-to-background uptake ratio as prognostic variables in all patients with STS was significant
Andersen KF, Fuglo HM, Rasmussen RM, et al. (Andersen et al., 2015b)	Retrospective	92	STS (55) Osteosarcoma (37)	High-grade	Upper extremity (16) Lower extremity (58) Trunk (26)	TLG and MTV ≥ 40%	High-significant accuracy of TLG and MTV as prognostic variables

BS: Bone sarcoma; STS: Soft tissue sarcoma; TLG: Total lesion glycolysis; MTV: Metabolic tumour volume; ROC: Receiver operating characteristic curve.

Table 2
Utility of PET/CT in evaluation of treatment response of sarcomas.

Author(s)	Threshold for histopathological response	Modality	No. of Patients	Histology	Grade	Location	Sensitivity	Specificity	Main Findings
Schuetze SM, Rubin BP, Vernon C, et al. (Schuetze, 2006)	≥40% decrease in tumour FDG-uptake	PET	46	Pleomorphic undifferentiated sarcoma (12) Synovial sarcoma (12) Leiomyosarcoma (11) Liposarcoma (4) Malignant peripheral nerve sheath tumour (3) Rhabdomyosarcoma (2) Fibrosarcoma (1) Myofibroblastic sarcoma (1)	All intermediate or high-grade	Upper extremity (16) Lower extremity (30)	–	–	Patients with a baseline tumour SUV_{max} ≥6 and < 40% decrease in FDG uptake were at high risk of systemic disease recurrence estimated to be 90% at 4 years from initial diagnosis
Evilevitch V, Weber WA, Tap WD, et al. (Evilevitch et al., 2008)	≥60% decrease in tumour FDG-uptake	PET/CT	42	NOS (12) Liposarcoma (9) Leiomyosarcoma (6) Synovial (5) Myxofibrosarcoma (4) MPNST (3) Other (3)	All high grade	Extremity (31) Retroperitoneal (10) Chest/ Trunk (5)	1.00	0.70	–
Benz MR, Czernin J, Tap WD, et al. (Benz et al., 2010b)	≥60% decrease in tumour FDG-uptake	PE/CT	12	Osteosarcoma (6) Ewing sarcoma (3) Dedifferentiated chondrosarcoma (2) Malignant giant cell tumour of the bone (1)	All high grade	–	0.75	0.88	Changes in FDG-SUV_{max} at the end of neoadjuvant treatment can identify histopathologic responders and non-responders in adult primary bone sarcoma patients
Eugene T, Corradini N, Carlier T, et al. (Eugene et al., 2012)	> 25% decrease in SUV	PET	21	GIST (17) STS (4)	–	–	0.80	0.90	FDG-PET is an early and sensitive method to evaluate an early response to Imatinib treatment
Byun BH, Kim SH, Lim SM, et al. (Byun et al., 2015)	Responders – Mean SUV of 2.5 Non-responders – Mean SUV of 3.5	PET	31	STS	Grade 2 (13) Grade 3 (18)	Extremity (21) Mediastinum (1) Retroperitoneal (2) Thyroid gland (1) Thoracic wall and axilla (2) Sinus maxillaris (1) Pelvic area (2)	0.60	0.70	Quantitative assessment of the ^{18}F-FDG kinetics in tumours should be used to measure the inhibitory effect of the chemotherapy on tumour growth
Tateishi U, Kawai A, Chuman H, et al. (Tateishi et al., 2011)	SUV reduction of ≤35%	PET/CT	42	Pleomorphic sarcoma (17) Myxoid liposarcoma (11) Myxofibrosarcoma (5) Leiomyosarcoma (3) Dedifferentiated liposarcoma (2) Fibrosarcoma (2) Epithelioid sarcoma (2) Alveolar soft part sarcoma (1)	All high-grade	Trunk (24) Extremities (18)	46.7	88.9	Metabolic reduction after NACT can be used for stratification of histopathologic response
Bajpai J, Kumar R, Sreenivas V, et al. (Bajpai et al., 2011)	Post-NACT and baseline-NACT SUV_{max} ratio (SUV_2:SUV_1) ≥0.48	PET/CT	31	Osteosarcoma (31)	All high grade	Femur (14) Fibula (1) Tibia (9) Clavicle (1) Scapula (1) Jaw (1) Ilium (1)	0.70	0.71	NACT response can be predicted reliably by PET-CT scan early in disease course

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Table 2 (*continued*)

Author(s)	Threshold for histopathological response	Modality	No. of Patients	Histology	Grade	Location	Sensitivity	Specificity	Main Findings
Gupta K, Pawaskar A, Basu S, et al. (Gupta et al., 2011)	$SUV_{max} \leq 6.84$	PET/CT	34	Ewing's sarcoma (54)	–	Femur (15) Tibia (11) Humerus (6) Pelvis (5) Scapula (5) Lung (4) Sacrum (3) Foot (2) Skull (2) Radius/ Ulna (1)	–	–	Significant correlation between change in metabolic activity of the primary tumour and histopathological response after neoadjuvant chemotherapy
Im HJ, Kim TS, Park SY, et al. (Im et al., 2012)	$SUV \geq 3$ g/ml MTV = 0 TLG ≥ 77.6g	PET/CT	20	Osteoblastic (19) Chondroblastic (1)	–	Femur (12) Tibia (3) Humerus (3) Pelvis (1) Mandible (1)	100 100 77.8	88.9 100 71.4	Metabolic/volumetric or metabolic indices after neoadjuvant chemotherapy were useful in predicting tumour responses

NACT: Neoadjuvant chemotherapy; MTV: Metabolic tumour volume; TLG: Total lesion glycolysis.

Herrmann et al., 2012). In the initial assessment of sarcomas, SUV_{max} in conjunction with presence and volume of necrosis as identified on FDG-PET/CT have shown to be strong prognostic factors for survival where high SUV_{max} indicates poor prognosis while a lower value indicates better prognosis (Herrmann et al., 2012; Fuglo et al., 2012). Specifically, STS patients with $SUV_{max} < 1.59$, 1.59 to 3.6 and at least 3.6 had 5-year recurrence-free survival rates of 66%, 24% and 11%, respectively (Schwarzbach et al., 2005). Furthermore, the presence and volume of necrosis identified on PET/CT after adjusting for SUV_{max} were shown to be strong independent adverse prognostic factors for disease recurrence and death in sarcoma patients (Fuglo et al., 2012). Likewise, the use of SUV_{max} has been shown to be a strong predictor of overall survival in patients with osseous sarcoma where patients with a $SUV_{max} \leq 5.8$ survived significantly longer than those with a $SUV_{max} > 5.8$ with a median survival time of 1265 and 656 days respectively (Hwang et al., 2016). Hence, SUV_{max} of the primary tumour has been shown to be a strong prognostic factor for survival. Overall, the significant correlation between SUV_{max} and tumour grading demonstrate the discriminative ability of FDG-SUV to differentiate low- from high-grade sarcomas, including liposarcoma, leiomyosarcoma, synovial sarcoma and peripheral nerve sheath tumour. Although FDG-PET/CT imaging is useful for distinguishing between low- and high-grade tumours, it may have limited usefulness for differentiating between low-grade and benign tumours (Rakheja et al., 2012).

The ability of FDG-PET/CT to identify treatment response is important for treatment planning of sarcoma patients. Despite responding to neoadjuvant chemotherapy, these tumours may not change significantly in size. These tumours may be composed of components that remain static to chemotherapeutic agents or are slow in response and size reduction, such as bone, cartilage and myxoid areas (Ha et al., 2017; Evilevitch et al., 2008; Benz et al., 2008). Being able to assess a patient's early response to chemotherapy may potentially guide management decisions (Table 2). While FDG-PET/CT scans are becoming an established component of cancer follow-up care, several studies have demonstrated that they could be an effective tool for directing treatment strategies early in patients' care (Piperkova et al., 2009). A study identified FDG-uptake as a sensitive predictor of histopathologic tumour response in STS with sensitivity and specificity of 100% and 67% respectively where a 35% reduction in tumour FDG-uptake at early follow-up following one cycle of chemotherapy was observed (Benz et al., 2009). Similarly, in osseous sarcoma, ≥60% decrease in FDG-uptake post-neoadjuvant treatment correctly classified 3 of 4 histopathologic responders as metabolic responders (sensitivity, 75%) and 7 of 8 histopathologic non-responders as metabolic non-responders (specificity, 88%), enabling the early identification of patients who will respond to treatment (Benz et al., 2010b). Hence, PET/CT imaging may be useful in detecting differential responses to neoadjuvant chemotherapeutic therapy, which will facilitate tailoring of post-operative therapy. Patients whose tumours show a significant drop in metabolic activity, according to SUV_{max}, following one cycle of chemotherapy may be encouraged to continue treatment in the face of adverse side effects. Notably, different methods were used within different studies for PET/CT-based differentiation of responders and non-responders influencing results of studies, including varying therapy protocols and timing of PET/CT imaging, thereby not allowing for comparison of different study results and drawing final conclusions. Nonetheless, these studies support additional prospective trials to establish whether changes in FDG-uptake following the start of treatment can be used to guide therapeutic decisions in sarcoma patients. Hence, FDG-PET/CT imaging has significant potential to identify patients with tumour resistance during the course of therapy that might benefit from treatment intensification or early resection. Additional studies are still required to further define the indications of PET/CT imaging in examination of treatment response and monitoring.

The use of PET/CT in staging (Table 3) and restaging (Table 4) is often reported in retrospective trials with heterogeneous results.

Table 3
Utility of PET/CT in staging of sarcomas.

Author(s)	Staging	Modality	No. of Patients	Subtypes	Sensitivity	Specificity	PPV	NPV	Accuracy	Impact on Management
Charest M, Hickeson M, Lisbona R, et al. (Charest et al., 2009)	Overall	PET/CT	212	STS (160) Osteosarcoma (52)	93.7 (STS) 94.6 (Osteosarcoma)	–	–	–	–	–
Fuglo HM, Jorgensen SM, Loft A, et al. (Fuglo et al., 2012)	M-staging N-staging	PET/CT	89	Synovial sarcoma (9) Liposarcoma (6) rhabdomyosarcoma (6) myxofibrosarcoma (5) Angiosarcoma (5) Leiomyosarcoma (4) Myofibrosarcoma (4) Extraskeletal osteosarcoma (4), Extraskeletal Ewing's sarcoma (4) Malignant peripheral nerve sheath tumour (3) Epitheloid sarcoma (3) Others (6)	0.95 1.00	0.96 0.90	0.87 0.27	0.98 1.00	0.95 0.91	3 patients with lymph nodes and 18 patients with distant metastases detected on PET/CT resulted in a change of treatment
Piperkova E, Mikhaeil M, Mousavi A (Piperkova et al., 2009)	Overall	CT PET PET/CT	93	Osteosarcoma (30) Leiomyosarcoma (27) Liposarcoma (16) Osteogenic sarcoma (15) Rhabdomyosarcoma (9) Fibrosarcoma (5) Synovial sarcoma (4), Chondrosarcoma (3) Haemangiosarcoma (3) GIST (3) Ewing sarcoma (2) Myofibrosarcoma (2) Schwannoma (2) Neroectodermal (1) Metastatic sarcoma from unknown origin (1)	1.00 0.97 1.00	0.92 1.00 1.00	0.97 1.00 1.00	1.00 0.92 1.00		–
Tateishi U, Kawai A, Chuman H, et al. (Tateishi et al., 2007)	 M-staging	PET PET/CT Combined Conventional PET PET/CT Combined	117	STS Osteosarcoma	– – – 0.65 0.90 0.92 0.96	– – – 0.90 0.91 0.91 0.91	– – – 0.82 0.88 0.88 0.88	– – – 0.78 0.93 0.94 0.97	0.70 0.83 0.87 0.79 0.91 0.91 0.93	PET/CT aided in the accurate staging of three (4%) patients and helped change tumour diagnosis from unresectable to resectable in two (2%) patients
Gerth HU, Juergens KU, Dirksen U, et al. (Gerth et al., 2007)	Overall	PET PET/CT	53	Ewing sarcoma (53)	0.71 0.87	0.95 0.97	– –	– –	0.88 0.94	PET/CT is significantly more accurate than PET alone for the detection and localization of lesions and improves staging for patients with Ewing tumour
Roberge D, Vakilian S, Alabed YZ, et al. (Roberge et al., 2012)	Overall M-staging	PET CT PET PET/CT	109	Leiomyosarcoma (17%) Liposarcoma (17%) Fibrosarcoma (16%) Synovial sarcoma (12%) MPNST (10%) Epithelioid (6%) Undifferentiated (16%) Other (7%)	0.52 0.82 78.6 0.80	0.96 0.76 92.8 0.86	0.78 – – –	0.89 – – –	0.88 – – –	5 patients (4.5%) were upstaged

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Table 3 (*continued*)

Author(s)	Staging	Modality	No. of Patients	Subtypes	Sensitivity	Specificity	PPV	NPV	Accuracy	Impact on Management
Lin H, Ozkan E, Erkan M, et al. (Lin et al., 2008)	Overall	PET	45	Angiosarcoma (2)	0.91 0.64		0.76	0.85	0.79	PET/CT altered patient management in 27% (12/45) of patients due to detection of unexpected metastases in 11 patients and identified a secondary primary (thyroid carcinoma) in 1 patient
		PET/CT		Chondrosarcoma (1)	0.98	0.96	0.97	0.98	0.97	
		PET/CT		Cystosarcoma (1)	1.00					
				Desmoid sarcoma (1)						
				Ewing sarcoma (3)						
				Fibrosarcoma (2)						
				Kaposi sarcoma (2)						
				Leiomyosarcoma (10)						
				Liposarcoma (5)						
	N-staging	Conventional		Osteosarcoma (11)	0.75	0.94	0.86	0.89	–	
		PET/CT		Pleomorphic sarcoma (1)	1.00	1.00	1.00	1.00		
	M-staging	Conventional Imaging		Rhabdomyosarcoma (1)	0.66	0.91	0.50	0.95	–	
				Spindle cell sarcoma (1)						
		PET/CT		Synovial sarcoma (2)	1.00	0.91	0.60	1.00	–	
				GIST (1)						
				Hemangiopericytoma (1)						
Iagaru A. Quon I, McDougall R, et al. (Iagaru et al., 2006)	Overall	PET/CT	44	Liposarcoma (1)	1.00	0.93	–	–	–	–
	M-staging	CT		Chondrosarcoma (3)	0.82	0.76	–	–	–	
		PET		Rhabdomyosarcoma (5)	0.79	0.93	–	–	–	
		PET/CT		Osteosarcoma (6)	0.80	0.86	–	–	–	
				Leiomyosarcoma (6)						
				Malignant fibrous histiocytoma (6) Ewing sarcoma (7) Otheres (10)						

STS: Soft tissue sarcoma; PPV: Positive predictive value; NPV: Negative predictive value.

Effective treatment stratification in sarcoma patients requires accurate assessment of the extent of primary tumour and evaluation for the presence of metastatic disease. The utility of FDG-PET/CT beyond conventional staging for the initial staging of sarcomas remains to be established. Several studies have evaluated the impact of incorporating FDG-PET/CT in the initial staging of various sarcomas subtypes and have reported it to be useful in identifying metastasis of musculoskeletal tumours. The overall TNM staging and M staging accuracies of PET/CT were also significantly higher than that of conventional imaging (Fuglo et al., 2012; Tateishi et al., 2007; Gerth et al., 2007). In a study of 117 patients who underwent staging for suspected bone or STS, FDG-PET scan was performed in addition to conventional imaging, such as bone scintigraphy, chest radiography and total body CT (Benz et al., 2009). PET/CT scanning demonstrated high sensitivity and specificity of up to 98% and 97% for detection of distant metastases and the predictive value of a positive or a negative test reached 97% and 98%, respectively in both bone and STS (Tateishi et al., 2007; Gerth et al., 2007). Furthermore, sensitivity and specificity were 100% and 90% for detection of lymph node metastases respectively (Fuglo et al., 2012). Consequently, the combined use of PET/CT modified the staging and altered management in up to 27% of osteosarcoma and STS patients, including liposarcoma, leiomyosarcoma and epithelioid sarcoma, due to detection of metastases (Fuglo et al., 2012). Similarly, a separate study comprising of 89 patients with osteosarcoma and STSS reported that PET/CT identified 3 patients with lymph nodes and 18 patients with distant metastases detected which resulted in a change of treatment (Hwang et al., 2016). In contrast, a few studies have shown limited impact on patient management with the use of routine FDG-PET/CT imaging for detecting metastatic disease in the initial staging for STS. A study of STS patients reported that no additional metastatic lesions were detected by metabolic imaging compared to CT imaging (Piperkova et al., 2009). Similarly, a separate study reported that PET/CT imaging were negative for distant disease in 91 STS cases (Roberge et al., 2012). Of the 14 positive scans, 6 patients were previously known to have metastases, 3 were false positives while 5 represented new findings of metastasis with a positive predictive value (PPV) of 79% (Roberge et al., 2012). These 5 patients (4.5%) were upstaged by FDG-PET/CT (Roberge et al., 2012). These studies suggest that routine use of FDG-PET/CT imaging as part of the initial staging of STS altered management in a limited number of patients. Overall, the utility of FDG-PET/CT for the initial staging of sarcoma remains to be clearly established where further prospective studies are needed to determine the added role of PET/CT imaging in specific subtypes. Although a high proportion of sarcoma are FDG-avid, use of routine PET/CT imaging for detection of metastatic disease as part of initial staging for sarcomas is not generally recommended as it alters management in few cases. PET/CT imaging may be recommended in sarcomas with greater risk of bone or retroperitoneal involvement as well as those with a greater probability of lymphatic involvement, such as myxoid liposarcoma, leiomyosarcoma, synovial sarcoma and rhabdomyosarcoma. This would aid in increasing the yield of staging by limiting its use to patients who are either at greater risk of systemic disease or expected to have a higher proportion of extrathoracic metastases.

Recurrent disease may be found in up to 80% of patients within the first 3 years following treatment, thus careful surveillance is required, particularly in higher-grade tumours or on the basis of clinical suspicion (Piperkova et al., 2009). PET/CT imaging has demonstrated in a few studies to be helpful in assessing possible local recurrence and performing restaging. In particular, PET/CT scans showed higher sensitivity and specificity in detection of local recurrence of 100% and 95.96% respectively in comparison with 97.2% and 63.5% for CT imaging (Piperkova et al., 2009). A separate study also showed that PET/CT had greater sensitivity and specificity of 94% and 78% respectively in the detection of recurrent bone or STS compared with CT alone (Byun et al., 2015). Similarly, additional studies demonstrated a high accuracy for FDG-PET/CT in detection of tumour recurrence with sensitivity and specificity of up to 96% and 81% respectively in bone and STS (Fuglo et al., 2012; Gerth et al., 2007; Eugene et al., 2012). As such, combined PET/CT imaging showed greater diagnostic accuracy in comparison with other conventional imaging in identification of recurrent disease. However, various benign processes may demonstrate increased glycolytic metabolism and FDG accumulation giving rise to false-positive results, such as infectious diseases, postsurgical and post-radiotherapy status as well as utilisation of granulocyte colony-stimulating factors (Al-Ibraheem et al., 2013). For example, high levels of FDG accumulation were reported in post-operative and post-traumatic inflammation, osteomyelitis as well as active granulomatous disease. Moreover, a study found evidence of avid FDG accumulation in

Table 4
Utility of PET/CT in restaging of sarcomas.

Author(s)	Staging	Modality	No. of Patients	Subtypes	Sensitivity	Specificity	PPV	NPV	Accuracy	Impact on Management
Piperkova E, Mikhaeil M, Mousavi A (Piperkova et al., 2009)	Overall	CT	93	Leiomyosarcoma (27) Liposarcoma (16) Osteogenic sarcoma (15) Rhabdomyosarcoma (9) Fibrosarcoma (5) Synovial sarcoma (4), Chondrosarcoma (3) Haemangiosarcoma (3) GIST (3) Ewing sarcoma (2) Myofibrosarcoma (2) Schwannoma (2) Neroectodermal (1) Metastatic sarcoma from unknown origin (1)	1.00	0.92	0.97	1.00		–
Gerth HU, Juergens KU, Dirksen U, et al. (Gerth et al., 2007)	Overall	PET	53	Ewing sarcoma (53)	0.71	0.95	–	–	0.88	PET/CT is significantly more accurate than PET alone for the detection and localization of lesions and improves staging for patients with Ewing tumour
		PET/CT			0.87	0.97	–	–	0.94	
Al-Ibraheem A, Buck AK, Benz MR, et al.	Overall	PET	43	Leiomyosarcoma (12) Liposarcoma (3) Malignant fibrous histiocytoma (2) Clear cell sarcoma (2) Synovial sarcoma (1) Rhabdomyosarcoma (1) Sarcoma NOS (1) Osteosarcoma (9) Ewing sarcoma (9) Chondrosarcoma (3)	0.67	0.88	0.90	0.61	0.74	Disease recurrence was detected in 6 patients exclusively by integrated FDG PET/CT which resulted in treatment modification
		PET/CT			0.89	0.88	0.92	0.82	0.88	
Sharma P, Khangembam BC, Suman KC, et al. (Sharma et al., 2013)	Overall	PET/CT	53	Ewing sarcoma (53)	0.95	0.87	0.90	0.93	0.92	FDG PET/CT demonstrates high diagnostic accuracy for detecting recurrence in patients with primary skeletal Ewing sarcoma, when it is suspected (clinically or on imaging) or during routine follow-up

PPV: Positive predictive value; NPV: Negative predictive value.

Table 5
Summary of recommendations of PET/CT imaging in sarcoma.

Utility of PET/ CT Imaging	Recommendations	Limitations
Tumour grading and prognostication	• Significant correlation between SUV_{max} and tumour grading as well as overall survival • Discriminative ability of tumour SUV to differentiate low- from high-grade sarcomas in suitable subtypes	• Limited usefulness in differentiating between low-grade and benign grade tumours
Evaluation of treatment response	• In STS, ≥60% decrease in FDG uptake resulted in sensitivity and specificity of 100% and 71% respectively for assessment of histopathologic response • In osseous sarcoma, ≥60% decrease in FDG uptake resulted in sensitivity and specificity of 75% and 88% respectively for assessment of metabolic responders	
Staging	• May be more useful for staging of sarcomas with a higher probability of metastases • Increases the yield of staging by limiting its use to patients who are either at greater risk of systemic disease or expected to have a higher proportion of extrathoracic metastases	• Largely retrospective studies • Contrasting results from studies obtained where PET/CT in the initial staging had limited impact on patient management
Restaging	• Superior sensitivity and specificity in detection of local recurrence compared to conventional imaging • High NPV on PET/CT imaging helps to exclude malignant deposits in abnormal findings	• Largely retrospective studies • Benign processes and tumours may demonstrate increased glycolytic metabolism and FDG accumulation giving rise to false-positive results

multiple benign tumours, including giant cell tumour, chondroblastoma and Langerhans cell histiocytosis (Sharma et al., 2013; Abouzied et al., 2005). Likewise, fibroxanthomas and cortical desmoid tumours may appear metabolically active on FDG-PET/CT imaging (Sharma et al., 2008). Conversely, various factors may contribute to false negative results, such as sarcoma grading and initial FDG-negative primaries. A study reported that the majority of these negative false tumours were interpreted as potentially low-grade sarcoma even when the size was greater than 5 cm (Tateishi et al., 2011). Hence, the need for correlative imaging is essential in these circumstances to accurately define lesions. A summary of recommendations has been included in Table 5, which highlights the utility of PET/ CT imaging in conjunction with limitations in the various aspects of sarcoma progression.

Moving forward, PET/CT imaging has the potential to yield additional information that could improve diagnosis and individually tailor cancer treatment. Several alternative PET radiopharmaceuticals are currently being investigated in pre-clinical and early clinical trials which have the potential to reveal biologically relevant tumour aspects, including growth rate, oxygen use and blood supply of tumours (Goodin et al., 2006). The use of PET may be extended with the use of other radiopharmaceuticals that are more specific than FDG for biologically relevant tumour aspects (Baur-Melnyk et al., 2008). Agents that report on aspects of tumours that contribute to tumour resistance and biologic aggressiveness are currently under study in the sarcoma patient population. For example, new PET tracers currently being investigated for use in sarcoma include ^{18}F-fluorothymidine (^{18}F-FLT) and ^{18}F-misonidazole (^{18}F-MISO) (Buck et al., 2008). ^{18}F-FLT is an analogue of the nucleotide thymidine and used as a marker of DNA synthesis. When used before and following treatment, ^{18}F-FLT may help determine the extent to which tumour growth is reduced in response to therapy (Buck et al., 2008). This is particularly relevant for sarcomas in which use of newer cytostatic agents leads to a slower rate of tumour growth rather than tumour reduction. Furthermore, ^{18}F-FLT-PET may allow changes in cell proliferation to be observed earlier and to a greater extent than^{18}FDG-PET (Pichler et al., 2008; Pfannenberg et al., 2007). ^{18}F-MISO is a marker of tumour hypoxia which is known to confer resistance to both radiotherapy and chemotherapy (Daftary, 2010; Frangioni, 2008). Hence, these novel radiopharmaceuticals in may play significant roles in the evaluation of treatment response in sarcoma patients.

5. Conclusion

In conclusion, PET/CT imaging provides useful complementary information that needs to be interpreted in the overall context of patients' clinical evaluation. PET/CT is an important contributor towards sarcoma grading, prognostication and evaluation of treatment response. The level of FDG-uptake of the primary tumour has prognostic implications, allowing the classification of tumour risk and selection of patients who may benefit from closer surveillance and more aggressive treatment. In selected clinical cases, PET/CT imaging may be recommended due to a large impact on clinical care, such as in sarcomas with greater risk of bone or retroperitoneal involvement or in those with a greater probability of lymphatic involvement. Nonetheless, larger prospective trials will be helpful to further establish the clinical value of PET/CT in sarcoma staging and restaging.

Declaration of Competing Interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.07.002.

References

Burningham, Z., Hashibe, M., Spector, L., Schiffman, J.D., 2012. The epidemiology of sarcoma. Clin. Sarcoma Res. 2, 14. https://doi.org/10.1186/2045-3329-2-14.
Martin Broto, J., Le Cesne, A., Reichardt, P., 2017. The importance of treating by histological subtype in advanced soft tissue sarcoma. Future Oncol. 13, 23–31. https://doi.org/10.2217/fon-2016-0500.
Mastrangelo, G., Coindre, J.M., Ducimetiere, F., Dei Tos, A.P., Fadda, E., Blay, J.Y., Buja, A., Fedeli, U., Cegolon, L., Frasson, A., Ranchere-Vince, D., Montesco, C., Ray-Coquard, I., et al., 2012. Incidence of soft tissue sarcoma and beyond: a population-based prospective study in 3 European regions. Cancer 118, 5339–5348. https://doi.org/10.1002/cncr.27555.
Ell, P.J., 2006. The contribution of PET/CT to improved patient management. Br. J. Radiol. 79, 32–36. https://doi.org/10.1259/bjr/18454286.
Mastrangelo, G., Fadda, E., Cegolon, L., Montesco, M.C., Ray-Coquard, I., Buja, A., Fedeli, U., Frasson, A., Spolaore, P., Rossi, C.R., 2010. A European project on incidence, treatment, and outcome of sarcoma. BMC Public Health 10, 188. https://doi.org/10.1186/1471-2458-10-188.
Choi, J.H., Moon, H., Park, J.Y., Byun, B.H., Lim, I., Kim, B.I., Choi, C.W., Lim, S.M., 2016. Comparison of diagnostic performances of FDG PET/CT and conventional imaging modalities in undifferentiated pleomorphic sarcoma. J. Nucl. Med. 57, 1574.
Zhu, A., Lee, D., Shim, H., 2011. Metabolic PET imaging in Cancer detection and therapy response. Semin. Oncol. 38, 55–69. https://doi.org/10.1053/j.seminoncol.2010.11.012.
McCarville, M.B., Christie, R., Daw, N.C., Spunt, S.L., Kaste, S.C., 2005. PET/CT in the evaluation of childhood sarcomas. AJR Am. J. Roentgenol. 184, 1293–1304. https://doi.org/10.2214/ajr.184.4.01841293.

Schuetze, S.M., 2006. Utility of positron emission tomography in sarcomas. Curr. Opin. Oncol. 18, 369–373. https://doi.org/10.1097/01.cco.0000228744.49294.12.

Lee, E.Y., Anthony, M.P., Leung, A.Y., Loong, F., Khong, P.L., 2012. Utility of FDG PET/CT in the assessment of myeloid sarcoma. AJR Am. J. Roentgenol. 198, 1175–1179. https://doi.org/10.2214/ajr.11.7743.

Mody, R.J., Bui, C., Hutchinson, R.J., Yanik, G.A., Castle, V.P., Frey, K.A., Shulkin, B.L., 2010. FDG PET imaging of childhood sarcomas. Pediatr. Blood Cancer 54, 222–227. https://doi.org/10.1002/pbc.22307.

Park, J.Y., Kim, E.N., Kim, D.Y., Suh, D.S., Kim, J.H., Kim, Y.M., Kim, Y.T., Nam, J.H., 2008. Role of PET or PET/CT in the post-therapy surveillance of uterine sarcoma. Gynecol. Oncol. 109, 255–262. https://doi.org/10.1016/j.ygyno.2008.01.030.

Brenner, W., Eary, J.F., Hwang, W., Vernon, C., Conrad, E.U., 2006. Risk assessment in liposarcoma patients based on FDG PET imaging. Eur. J. Nucl. Med. Mol. Imaging 33, 1290–1295. https://doi.org/10.1007/s00259-006-0170-y.

Kumar, R., Chauhan, A., Vellimana, A.K., Chawla, M., 2006. Role of PET/PET–CT in the management of sarcomas. Expert Rev. Anticancer Ther. 6, 1241–1250. https://doi.org/10.1586/14737140.6.8.1241.

Ioannidis, J.P., Lau, J., 2003. 18F-FDG PET for the diagnosis and grading of soft-tissue sarcoma: a meta-analysis. J. Nucl. Med. 44, 717–724.

Muheremu, A., Ma, J., Amudong, A., Ma, Y., Niyazi, M., Ou, Y., Ma, Y., 2017. Positron emission tomography/computed tomography for osseous and soft tissue sarcomas: a systematic review of the literature and meta-analysis. Mol. Clin. Oncol. 7, 461–467. https://doi.org/10.3892/mco.2017.1329.

Rodríguez-Alfonso, B., Mucientes Rasilla, J., Mitjavila Casanovas, M., Cardona Arboniés, J., Cubedo, R., 2014. < Span class = "elsevierStyleSup" > 18 < /span > F-FDG–PET–CT in soft tissue sarcomas: when to image? Revista Española de Medicina Nuclear e Imagen Molecular (English Edition) 33, 43–49. https://doi.org/10.1016/j.remnie.2013.11.005.

Toner, G.C., Hicks, R.J., 2008. PET for sarcomas other than gastrointestinal stromal tumors. Oncologist 13, 22–26. https://doi.org/10.1634/theoncologist.13-S2-22.

Gabriel, M., Rubello, D., 2016. 18F-FDG PET-CT in soft tissue sarcomas: staging, restaging, and prognostic value? Nucl. Med. Commun. 37, 3–8. https://doi.org/10.1097/mnm.0000000000000407.

Kandathil, A., Subramaniam, R.M., 2019. PET/Computed tomography and precision medicine. PET Clin. 12, 475–488. https://doi.org/10.1016/j.cpet.2017.05.005.

Norman, G., Fayter, D., Lewis-Light, K., Chisholm, J., McHugh, K., Levine, D., Jenney, M., Mandeville, H., Gatz, S., Phillips, B., 2015. An emerging evidence base for PET-CT in the management of childhood rhabdomyosarcoma: systematic review. BMJ Open 5, e006030. https://doi.org/10.1136/bmjopen-2014-006030.

Kassem, T.W., Abdelaziz, O., Emad-Eldin, S., 2017. Diagnostic value of (18)F-FDG-PET/CT for the follow-up and restaging of soft tissue sarcomas in adults. Diagn. Interv. Imaging 98, 693–698. https://doi.org/10.1016/j.diii.2017.06.006.

Benz, M.R., Dry, S.M., Eilber, F.C., Allen-Auerbach, M.S., Tap, W.D., Elashoff, D., Phelps, M.E., Czernin, J., 2010a. Correlation between glycolytic phenotype and tumor grade in soft-tissue sarcomas by 18F-FDG PET. J. Nucl. Med. 51, 1174–1181. https://doi.org/10.2967/jnumed.109.074229.

Fendler, W.P., Chalkidis, R.P., Ilhan, H., Knösel, T., Herrmann, K., Issels, R.D., Bartenstein, P., Cyran, C.C., Lindner, L.H., Hacker, M., 2015. Evaluation of several FDG PET parameters for prediction of soft tissue tumour grade at primary diagnosis and recurrence. Eur. Radiol. 25, 2214–2221. https://doi.org/10.1007/s00330-015-3654-y.

Tateishi, U., Yamaguchi, U., Seki, K., Terauchi, T., Arai, Y., Hasegawa, T., 2006. Glut-1 expression and enhanced glucose metabolism are associated with tumour grade in bone and soft tissue sarcomas: a prospective evaluation by [18F]fluorodeoxyglucose positron emission tomography. Eur. J. Nucl. Med. Mol. Imaging 33, 683–691. https://doi.org/10.1007/s00259-005-0044-8.

Charest, M., Hickeson, M., Lisbona, R., Novales-Diaz, J.A., Derbekyan, V., Turcotte, R.E., 2009. FDG PET/CT imaging in primary osseous and soft tissue sarcomas: a retrospective review of 212 cases. Eur. J. Nucl. Med. Mol. Imaging 36, 1944–1951. https://doi.org/10.1007/s00259-009-1203-0.

Rakheja, R., Makis, W., Skamene, S., Nahal, A., Brimo, F., Azoulay, L., Assayag, J., Turcotte, R., Hickeson, M., 2012. Correlating metabolic activity on 18F-FDG PET/CT with histopathologic characteristics of osseous and soft-tissue sarcomas: a retrospective review of 136 patients. AJR Am. J. Roentgenol. 198, 1409–1416. https://doi.org/10.2214/ajr.11.7560.

Schwarzbach, M.H.M., Hinz, U., Dimitrakopoulou-Strauss, A., Willeke, F., Cardona, S., Mechtersheimer, G., Lehnert, T., Strauss, L.G., Herfarth, C., Büchler, M.W., 2005. Prognostic significance of preoperative [18-F] fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging in patients with resectable Soft tissue sarcomas. Ann. Surg. 241, 286–294. https://doi.org/10.1097/01.sla.0000152663.61348.6f.

Herrmann, K., Benz, M.R., Czernin, J., Allen-Auerbach, M.S., Tap, W.D., Dry, S.M., Schuster, T., Eckardt, J.J., Phelps, M.E., Weber, W.A., Eilber, F.C., 2012. (18)F-FDG-PET/CT imaging as an early survival predictor in patients with primary high-grade Soft tissue sarcomas undergoing neoadjuvant therapy. Clin. Cancer Res. 18, 2024–2031. https://doi.org/10.1158/1078-0432.CCR-11-2139.

Fuglo, H.M., Jorgensen, S.M., Loft, A., Hovgaard, D., Petersen, M.M., 2012. The diagnostic and prognostic value of (1)(8)F-FDG PET/CT in the initial assessment of high-grade bone and soft tissue sarcoma. A retrospective study of 89 patients. Eur. J. Nucl. Med. Mol. Imaging 39, 1416–1424. https://doi.org/10.1007/s00259-012-2159-z.

Hwang, J.P., Lim, I., Kong, C.B., Jeon, D.G., Byun, B.H., Kim, B.I., Choi, C.W., Lim, S.M., 2016. Prognostic value of SUVmax measured by pretreatment Fluorine-18 fluorodeoxyglucose positron emission Tomography/Computed tomography in patients with ewing sarcoma. PLoS One 11, e0153281. https://doi.org/10.1371/journal.pone.0153281.

Ha, S.C., Oh, J.S., Roh, J.L., Moon, H., Kim, J.S., Cho, K.J., Choi, S.H., Nam, S.Y., Kim, S.Y., 2017. Pretreatment tumor SUVmax predicts disease-specific and overall survival in patients with head and neck soft tissue sarcoma. Eur. J. Nucl. Med. Mol. Imaging 44, 33–40. https://doi.org/10.1007/s00259-016-3456-8.

Evilevitch, V., Weber, W.A., Tap, W.D., Allen-Auerbach, M., Chow, K., Nelson, S.D., Eilber, F.R., Eckardt, J.J., Elashoff, R.M., Phelps, M.E., Czernin, J., Eilber, F.C., 2008. Reduction of glucose metabolic activity is more accurate than change in size at predicting histopathologic response to neoadjuvant therapy in high-grade soft-tissue sarcomas. Clin. Cancer Res. 14, 715–720. https://doi.org/10.1158/1078-0432.Ccr-07-1762.

Benz, M.R., Allen-Auerbach, M.S., Eilber, F.C., Chen, H.J., Dry, S., Phelps, M.E., Czernin, J., Weber, W.A., 2008. Combined assessment of metabolic and volumetric changes for assessment of tumor response in patients with soft-tissue sarcomas. J. Nucl. Med. 49, 1579–1584. https://doi.org/10.2967/jnumed.108.053694.

Piperkova, E., Mikhaeil, M., Mousavi, A., Libes, R., Viejo-Rullan, F., Lin, H., Rosen, G., Abdel-Dayem, H., 2009. Impact of PET and CT in PET/CT studies for staging and evaluating treatment response in bone and soft tissue sarcomas. Clin. Nucl. Med. 34, 146–150. https://doi.org/10.1097/RLU.0b013e3181966f9d.

Benz, M.R., Czernin, J., Allen-Auerbach, M.S., Tap, W.D., Dry, S.M., Elashoff, D., Chow, K., Evilevitch, V., Eckardt, J.J., Phelps, M.E., Weber, W.A., Eilber, F.C., 2009. FDG-PET/CT imaging predicts histopathologic treatment responses after the initial cycle of neoadjuvant chemotherapy in high-grade soft-tissue sarcomas. Clin. Cancer Res. 15, 2856–2863. https://doi.org/10.1158/1078-0432.Ccr-08-2537.

Benz, M.R., Czernin, J., Tap, W.D., Eckardt, J.J., Seeger, L.L., Allen-Auerbach, M.S., Dry, S.M., Phelps, M.E., Weber, W.A., Eilber, F.C., 2010b. FDG-PET/CT imaging predicts histopathologic treatment responses after neoadjuvant therapy in adult primary bone sarcomas. Sarcoma 2010, 7. https://doi.org/10.1155/2010/143540.

Tateishi, U., Yamaguchi, U., Seki, K., Terauchi, T., Arai, Y., Kim, E.E., 2007. Bone and soft-tissue sarcoma: preoperative staging with fluorine 18 fluorodeoxyglucose PET/CT and conventional imaging. Radiology 245, 839–847. https://doi.org/10.1148/radiol.2453061538.

Gerth, H.U., Juergens, K.U., Dirksen, U., Gerss, J., Schober, O., Franzius, C., 2007. Significant benefit of multimodal imaging: PET/CT compared with PET alone in staging and follow-up of patients with Ewing tumors. J. Nucl. Med. 48, 1932–1939. https://doi.org/10.2967/jnumed.107.045286.

Roberge, D., Vakilian, S., Alabed, Y.Z., Turcotte, R.E., Freeman, C.R., Hickeson, M., 2012. FDG PET/CT in initial staging of adult soft-tissue sarcoma. Sarcoma 2012, 960194. https://doi.org/10.1155/2012/960194.

Byun, B.H., Kim, S.H., Lim, S.M., Lim, I., Kong, C.B., Song, W.S., Cho, W.H., Jeon, D.G., Lee, S.Y., Koh, J.S., Chung, S.K., 2015. Prediction of response to neoadjuvant chemotherapy in osteosarcoma using dual-phase (18)F-FDG PET/CT. Eur. Radiol. 25, 2015–2024. https://doi.org/10.1007/s00330-015-3609-3.

Eugene, T., Corradini, N., Carlier, T., Dupas, B., Leux, C., Bodet-Milin, C., 2012. (1)(8)F-FDG-PET/CT in initial staging and assessment of early response to chemotherapy of pediatric rhabdomyosarcomas. Nucl. Med. Commun. 33, 1089–1095. https://doi.org/10.1097/MNM.0b013e328356741f.

Al-Ibraheem, A., Buck, A.K., Benz, M.R., Rudert, M., Beer, A.J., Mansour, A., Pomykala, K.L., Haller, B., Juenger, H., Scheidhauer, K., Schwaiger, M., Herrmann, K., 2013. (18) F-fluorodeoxyglucose positron emission tomography/computed tomography for the detection of recurrent bone and soft tissue sarcoma. Cancer. 119, 1227–1234. https://doi.org/10.1002/cncr.27866.

Sharma, P., Khangembam, B.C., Suman, K.C., Singh, H., Rastogi, S., Khan, S.A., Bakhshi, S., Thulkar, S., Bal, C., Malhotra, A., Kumar, R., 2013. Diagnostic accuracy of 18F-FDG PET/CT for detecting recurrence in patients with primary skeletal Ewing sarcoma. Eur. J. Nucl. Med. Mol. Imaging 40, 1036–1043. https://doi.org/10.1007/s00259-013-2388-9.

Abouzied, M.M., Crawford, E.S., Nabi, H.A., 2005. 18F-FDG imaging: pitfalls and artifacts. J. Nucl. Med. Technol. 33, 145–155 quiz 62-3. doi:.

Sharma, N., Neumann, D., Macklis, R., 2008. The impact of functional imaging on radiation medicine. Radiat. Oncol. 3, 25. https://doi.org/10.1186/1748-717x-3-25.

Goodin, G.S., Shulkin, B.L., Kaufman, R.A., McCarville, M.B., 2006. PET/CT characterization of fibroosseous defects in children: 18F-FDG uptake can mimic metastatic disease. AJR Am. J. Roentgenol. 187, 1124–1128. https://doi.org/10.2214/ajr.06.0171.

Baur-Melnyk, A., Buhmann, S., Becker, C., Schoenberg, S.O., Lang, N., Bartl, R., Reiser, M.F., 2008. Whole-body MRI versus whole-body MDCT for staging of multiple myeloma. Am. J. Roentgenol. 190, 1097–1104. https://doi.org/10.2214/AJR.07.2635.

Buck, A.K., Herrmann, K., Buschenfelde, C.M., Juweid, M.E., Bischoff, M., Glatting, G., Weirich, G., Moller, P., Wester, H.J., Scheidhauer, K., Dechow, T., Peschel, C., Schwaiger, M., et al., 2008. Imaging bone and soft tissue tumors with the proliferation marker [18F]fluorodeoxythymidine. Clin. Cancer Res. 14, 2970–2977. https://doi.org/10.1158/1078-0432.Ccr-07-4294.

Pichler, B., Wehrl, H.F., Kolb, A., Judenhofer, M.S., 2008. PET/MRI: THE NEXT GENERATION OF MULTI-MODALITY IMAGING? Semin. Nucl. Med. 38, 199–208. https://doi.org/10.1053/j.semnuclmed.2008.02.001.

Pfannenberg, A.C., Aschoff, P., Brechtel, K., Muller, M., Klein, M., Bares, R., Claussen, C.D., Eschmann, S.M., 2007. Value of contrast-enhanced multiphase CT in combined PET/CT protocols for oncological imaging. Br. J. Radiol. 80, 437–445. https://doi.org/10.1259/bjr/34082277.

Daftary, A., 2010. PET-MRI: challenges and new directions. Indian J. Nucl. Med. 25, 3–5. https://doi.org/10.4103/0972-3919.63590.

Frangioni, J.V., 2008. New technologies for human cancer imaging. J. Clin. Oncol. 26, 4012–4021. https://doi.org/10.1200/jco.2007.14.3065.

Rakheja, R., Makis, W., Tulbah, R., Skamene, S., Holcroft, C., Nahal, A., Turcotte, R., Hickeson, M., 2013. Necrosis on FDG PET/CT correlates with prognosis and mortality in sarcomas. AJR Am. J. Roentgenol. 201, 170–177. https://doi.org/10.2214/ajr.12.9795.

Hoshi, M., Oebisu, N., Takada, J.U.N., Ieguchi, M., Wakasa, K., Nakamura, H., 2014. Role of FDG-PET/CT for monitoring soft tissue tumors. Oncol. Lett. 7, 1243–1248. https://doi.org/10.3892/ol.2014.1876.

Choi, E.S., Ha, S.G., Kim, H.S., Ha, J.H., Paeng, J.C., Han, I., 2013. Total lesion glycolysis by 18F-FDG PET/CT is a reliable predictor of prognosis in soft-tissue sarcoma. Eur. J. Nucl. Med. Mol. Imaging 40, 1836–1842. https://doi.org/10.1007/s00259-013-2511-y.

Skamene, S.R., Rakheja, R., Dahlstrom, K.R., Roberge, D., Nahal, A., Charest, M., Turcotte, R., Hickeson, M., Freeman, C., 2014. Metabolic activity measured on PET/CT correlates with clinical outcomes in patients with limb and girdle sarcomas. J. Surg. Oncol. 109, 410–414. https://doi.org/10.1002/jso.23523.

Andersen, K.F., Fuglo, H.M., Rasmussen, S.H., Petersen, M.M., Loft, A., 2015a. Semi-quantitative calculations of primary tumor metabolic activity using F-18 FDG PET/CT as a predictor of survival in 92 patients with high-grade bone or Soft tissue sarcoma. Bull. Sch. Med. Md 94, e1142. https://doi.org/10.1097/md.0000000000001142.

Andersen, K.F., Fuglo, H.M., Rasmussen, S.H., Petersen, M.M., Loft, A., 2015b. Volume-based F-18 FDG PET/CT imaging markers provide supplemental prognostic information to histologic grading in patients with high-grade bone or Soft tissue sarcoma. Medicine 94, e2319. https://doi.org/10.1097/MD.0000000000002319.

Iagaru, A., Quon, A., McDougall, I.R., Gambhir, S.S., 2006. F-18 FDG PET/CT evaluation of osseous and soft tissue sarcomas. Clin. Nucl. Med. 31, 754–760. https://doi.org/10.1097/01.rlu.0000246846.01492.31.

Tateishi, U., Kawai, A., Chuman, H., Nakatani, F., Beppu, Y., Seki, K., Miyake, M., Terauchi, T., Moriyama, N., Kim, E.E., 2011. PET/CT allows stratification of responders to neoadjuvant chemotherapy for high-grade sarcoma: a prospective study. Clin. Nucl. Med. 36, 526–532. https://doi.org/10.1097/RLU.0b013e3182175856.

Bajpai, J., Kumar, R., Sreenivas, V., Sharma, M.C., Khan, S.A., Rastogi, S., Malhotra, A., Gamnagatti, S., Kumar, R., Safaya, R., Bakhshi, S., 2011. Prediction of chemotherapy response by PET-CT in osteosarcoma: correlation with histologic necrosis. J. Pediatr. Hematol. Oncol. 33, e271–8. https://doi.org/10.1097/MPH.0b013e31820ff78e.

Gupta, K., Pawaskar, A., Basu, S., Rajan, M.G., Asopa, R.V., Arora, B., Nair, N., Banavali, S., 2011. Potential role of FDG PET imaging in predicting metastatic potential and assessment of therapeutic response to neoadjuvant chemotherapy in Ewing sarcoma family of tumors. Clin. Nucl. Med. 36, 973–977. https://doi.org/10.1097/RLU.0b013e31822f684b.

Im, H.J., Kim, T.S., Park, S.Y., Min, H.S., Kim, J.H., Kang, H.G., Park, S.E., Kwon, M.M., Yoon, J.H., Park, H.J., Kim, S.K., Park, B.K., 2012. Prediction of tumour necrosis fractions using metabolic and volumetric 18F-FDG PET/CT indices, after one course and at the completion of neoadjuvant chemotherapy, in children and young adults with osteosarcoma. Eur. J. Nucl. Med. Mol. Imaging 39, 39–49. https://doi.org/10.1007/s00259-011-1936-4.

Lin, H., Ozkan, E., Erkan, M., Viejo-Rullan, F., Mikhaeil, M., Mosavi, A., Piperkova, E., Libes, R., Rosen, G., Abdel-Dayem, H., 2008. Incremental value of FDG PET/CT in initial staging of patients (pts) with bone and soft tissue sarcoma (BSTS). J. Nucl. Med. 49, 149P.