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Added value of ^{18}F-FDG PET-CT in staging of Ewing sarcoma in children and young adults

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Abstract

Background: Ewing sarcoma (ES) is currently staged using Radiography, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and skeletal scintigraphy (bone scan). ^{18}F- fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET-CT) is increasingly used for staging and follow-up, but its role is still under evaluation.

Objective: To evaluate the added information from ^{18}F-FDG PET-CT studies compared to conventional imaging and to estimate radiation doses received from radiological and nuclear medicine imaging during staging of Ewing sarcoma.

Material and methods: Sixty-one patients under the age of 30 years (mean 16, range 5–26) were diagnosed with Ewing sarcoma in Norway during the period 2005–2012. Nineteen patients met the inclusion criteria for this population-based study: pre therapeutic ^{18}F-FDG PET-CT and a minimum follow-up of 12 months. Imaging reports, medical records and pathology reports were collected and compared for all patients. Biopsy histology, supplementary imaging and long-term follow-up (median 27 months) were taken as composite gold standard.

Results: ^{18}F-FDG PET-CT detected more lesions than conventional imaging in four patients (21%) but this did not change planned treatment as they all had extensive metastatic disease. The ^{18}F-FDG PET-CT study was false negative in one patient and showed false positive lesions in three patients (16%). The estimated mean (range) effective total radiation dose was from CT: 7 mSv (2–16), skeletal scintigraphy: 3 mSv (0–5) and ^{18}F-FDG PET-CT: 5 mSv (4–6).

Conclusion: ^{18}F-FDG PET-CT is useful for staging of Ewing sarcoma and increase detection of metastases. False positive lesions are quite common, emphasizing the need for supplementary imaging or biopsy of suspected FDG positive metastases.

Keywords: Ewing sarcoma, ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT), Radiation dose, Adolescents, Children, Staging

Introduction

Ewing sarcoma is a rare malignant tumour arising from neuroectodermal-derived cells in bone or soft tissue. The Ewing sarcoma family of tumours comprises the four tumour entities: Ewing sarcoma of bone, extra skeletal Ewing sarcoma, Primitive Neuroectodermal Tumour (PNET), and Askin tumour (Murphey et al., 2013). Histological examination of a biopsy specimen with detection of a specific fusion transcript

involving the Ewing sarcoma RNA (ribonucleic acid) binding protein 1 gene (EWSR1 gene; Ewing sarcoma breakpoint region 1) is mandatory for diagnosis (Potratz et al., 2012). Ewing sarcoma constituted 1.6% of all cancers in Norwegian children below 15 years of age in the period 1985–2015 (Nasjonalt kvalitetsregister for barnekreft, Kreftregisteret, 2015). Median age at presentation was 14 years (Helsedirektoratet Avdeling sykehustjenester Oslo Norway, 2015). Patients with local disease have a five-year survival rate of 65–75%, which has improved over the last decades (Group EESNW, 2014; Gaspar et al., 2015). 25% of the patients will have detectable metastases at presentation (Potratz et al., 2012). With the presence of pulmonary metastases five-year survival is reduced to 30% while patients with both pulmonary and skeletal metastases have a five-year survival rate of less than 10% (Helsedirektoratet Avdeling sykehustjenester Oslo Norway, 2015). In addition to the presence of metastases, the most important negative prognostic factors are: large tumour volume, high serum lactate dehydrogenase (LDH) levels, tumour in axial skeleton and age > 15 years (Group EESNW, 2014). Correct staging of the disease is paramount to correct treatment allocation. The Norwegian National Guidelines (Helsedirektoratet Avdeling sykehustjenester Oslo Norway, 2015) are largely based on protocols from the Italian and Scandinavian Sarcoma Groups (ISG/SSG) (Italian Sarcoma Group (Bologna Italy), Scandinavian Sarcoma Group (Oncologic Center Lund Sweden), 1999a; Italian Sarcoma Group (Bologna Italy), Scandinavian Sarcoma Group (Oncologic Center Lund Sweden), 1999b) and recommend a combination of some, or all, of the following imaging modalities for staging of Ewing Sarcoma: Radiography, ultrasound, CT, MRI, skeletal scintigraphy with ^{99m}Tc- labelled bisphosphonates (bone scan) and ^{18}F- FDG PET-CT. Radiography, CT and MRI of tumour site, affected limb and adjacent joints, and skeletal scintigraphy are considered mandatory examinations while ultrasound of tumour site, angiography of affected limb, abdominal CT (in patients with lesions not involving the abdomen) and ^{18}F-FDG PET-CT are optional.

The use of ^{18}F-FDG PET-CT in staging, restaging and assessment of therapy response in patients with Ewing sarcoma is increasing worldwide even though the method at present is not considered a standard examination in the diagnostic work-up of these patients (Group EESNW, 2014; Biermann et al., 2017). PET imaging with ^{18}F-FDG depicts upregulated glucose metabolism in cancer cells in Ewing sarcoma as well as in other solid tumours. Maximum standard uptake value (SUVmax) in Ewing sarcoma tumours is highly variable ranging from 3 to 21 (Charest et al., 2009) and 2–11 (Quartuccio et al., 2015) in different series. Highly aggressive, fast growing tumours (higher -grade tumours) usually demonstrate more intense ^{18}F-FDG uptake than lower grade tumours. This can be used to target biopsy to the most metabolic active area of a given tumour and to characterise indeterminate lesions (Lakkaraju et al., 2010). In a recently published study, Palmerini et al., found that SUV_{max} of primary tumours predicted outcome (event free survival) in patients with Ewing sarcoma and they suggest that it may be used as a prognostic factor along with other prognostic factors such as tumour size, localisation of primary tumour and patient age (Palmerini et al., 2017). Dedicated paediatric PET-CT protocols which include individual weight-based activities of ^{18}F-FDG (Lassmann & Treves, 2014) and low dose CT, are established at all the PET sites in Norway. Despite using child specific PET-CT protocols, patients will

receive an effective radiation dose of 8 mSv to 13 mSv from a single investigation (Alessio et al., 2009), the CT component contributing to 40%.

The aims of this national population-based study were to evaluate the potential benefit of ^{18}F-FDG PET-CT in staging of patients with Ewing sarcoma, and to examine to which degree information from ^{18}F-FDG PET-CT affected the treatment decisions. We also estimated the radiation doses received by the patients during diagnostic work-up including the contribution from ^{18}F-FDG PET-CT.

Material and methods

Patient population

Data from patients diagnosed with Ewing sarcoma in Norway between January 1st 2005 and December 31st 2012 were retrospectively analysed. The inclusion criteria were: diagnosed with Ewing sarcoma during the period 01.01.05–31.12.12, below 30 years of age at the time of diagnosis, ^{18}F-FDG PET-CT performed before treatment and a minimum follow-up time of 12 months after diagnosis. Seventy-six patients were identified from the Scandinavian Sarcoma register in Lund, Sweden which is managed by the Scandinavian Sarcoma group (Scandinavian Sarcoma Group, 1979). Sixty-one patients were below 30 years of age. Nineteen patients had a pre therapeutic ^{18}F-FDG PET-CT and minimum follow-up time of 12 months and were included in the study. Depending on the extent of disease at diagnosis, the patients in our study were allocated to one of two Italian- Norwegian joint study protocols: ISG/SSG III and ISG/SSG IV (Italian Sarcoma Group (Bologna Italy), Scandinavian Sarcoma Group (Oncologic Center Lund Sweden), 1999a; Italian Sarcoma Group (Bologna Italy), Scandinavian Sarcoma Group (Oncologic Center Lund Sweden), 1999b), or to Euro Ewing 2008 (Group EES, 2010). Medical records, pathology results and all pre therapeutic imaging reports were collected for each patient. All ^{18}F-FDG PET-CT studies have been performed at PET-CT scanners located at the Oslo University Hospital or Haukeland University Hospital.

Imaging

Imaging reports from pre therapeutic ^{18}F-FDG PET-CT examinations were compared with those from conventional imaging (ultrasound, Radiography, CT, MRI, skeletal scintigraphy). Since many patients are examined for several weeks until the diagnosis of Ewing sarcoma is finally proven by biopsy, we included all reports from imaging performed four months prior to, and 1 month after, the date of the pre therapeutic ^{18}F -FDG PET-CT study. The skeletal scintigraphies consisted of planar images from skull to feet at one or several time points after injection, supplemented with Single Photon Emission Tomography CT (SPECT-CT) in two patients. The ^{18}F-FDG PET-CT examinations were performed from skull to feet with arms above the head approximately 60 min after intravenous administration of ^{18}F-FDG. The information from all pre therapeutic imaging was compared with information from subsequent imaging, histology examinations of operation specimens and medical reports during a minimum of 12 months of follow-up.

Dose estimations

Conventional imaging (ultrasound, Radiography, CT, MRI, skeletal scintigraphy) were performed at various sites: local hospitals, regional hospitals, and university hospitals in Norway. All CT examinations (type and number) and skeletal scintigraphies (number) were recorded for each patient. Effective radiation doses from standardized CT examination (Siemens, 2006) were estimated using the software CT-Expo (Stamm & Nagel, 2002). The patient data were matched to mathematical phantoms corresponding to an average new-born, 6-year-old, or adult. Patient weight was approximated by percentile growth curves for different age categories (Júliusson et al., 2009) and adapted to the available phantom sizes. For the nuclear medicine imaging procedures, maximum injected activity followed the European Association of Nuclear Medicine (EANM) paediatric dosage card recommendation (Lassmann & Treves, 2014). A nuclear medicine radiation dose tool (SNMI) based on the bio kinetic model of radiopharmaceutical distribution issued by the International Commission on Radiological Protection (ICRP 106) (ICRP, 2008), was applied and effective doses estimated for mathematical phantoms corresponding to an average 1-, 5-, 10-, 15- year-old, or adult.

Compliance with ethical standards

Informed consent for registration in the National Sarcoma Register at Oslo University Hospital was obtained for all study patients. The study was approved as a quality-control study by the Regional Medical Ethics Committee of Western Norway and the local Data Protection officer.

Results

Patient characteristics

Nineteen patients met the inclusion criteria of this study (Fig. 1). Patient characteristics including stage of disease at diagnosis, amount of pre therapeutic conventional imaging and SUV_{max} of primary tumour are listed in Table 1. Mean age of the patients was 16 years (range 5–26 years). Mean follow-up was 33 months (range 5–62 months; median 27 months). One patient died 5 months after diagnosis. The primary tumours were located in the skull ($n = 1$), upper extremity (n = 1), rib ($n = 5$), spine (n = 1), pelvis ($n = 4$) or lower extremity ($n = 3$). Three patients had Ewing sarcoma originating from soft tissue. In one patient with multiple skeletal metastases at diagnosis, the primary tumour site remained unknown. Eight patients in our cohort had metastases at diagnosis. None of the remaining 11 patients developed metastases during follow-up. At the end of the study period, December 31st 2013, four of 19 patients had died of the disease and one patient with metastases had progression of disease. The remaining 14 patients were alive and considered free of disease.

Imaging

There was full concordance between conventional imaging modalities and ^{18}F-FDG PET-CT regarding localization of primary tumour in 16 patients (84%) and regarding metastases in 11 patients (58%), respectively. Discrepancies in localization of primary tumour could not be evaluated in two patients due to partly removal of tumour before initial ^{18}F-FDG PET-CT in one patient, and undetectable primary tumour site in the

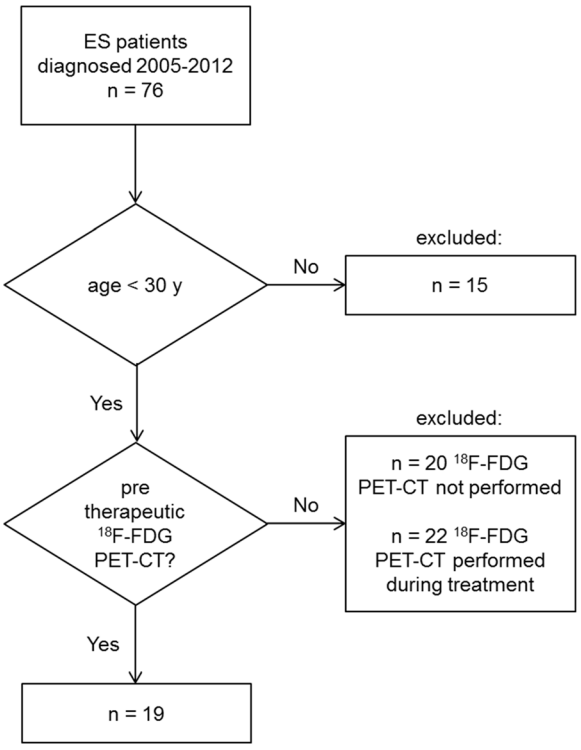

Fig. 1 Study population: Patients diagnosed with Ewing sarcoma in Norway from 2005 to 2012

other patient. Conventional imaging modalities and ^{18}F-FDG PET-CT differed both regarding primary tumour site and metastases in one patient (tumour and skeletal metastases did not have increased FDG uptake) and regarding metastases in another seven patients. Four ^{18}F-FDG PET-CT studies (21%) detected true FDG positive metastases not found by conventional imaging, one study was false negative due to lack of FDG uptake and three studies showed false FDG positive lesions. The added true FDG positive lesions found by the ^{18}F-FDG PET-CT examinations in four patients did not lead to any changes in the already planned treatment based on information from conventional imaging as they all had extensive metastatic disease.

Dose estimations

The pre therapeutic imaging consisted of 1–3 CT examinations (mean 2), 0–1 skeletal scintigraphy (mean 1) and one ^{18}F-FDG PET-CT examination per patient. Estimated mean effective dose from CT was: 7 mSv (range 2–16), skeletal scintigraphy: 3 mSv (0–5), and ^{18}F-FDG PET-CT: 5 mSv (4–6), respectively. Total estimated effective dose from all pre therapeutic imaging, was 15 mSv (8–24). Estimated dose contribution from CT, skeletal scintigraphy and ^{18}F-FDG PET-CT for each of the 19 patients are shown in Fig. 2.

Discussion

In this population-based national cohort of children and young adults diagnosed with Ewing sarcoma during the period 2005–2012, we found that ^{18}F-FDG PET-CT detected

Table 1 Patient characteristics

Patient number	Stage of disease	Imaging modalities for comparison	SUV_{max} primary tumour	Discrepancy between conventional imaging and ^{18}F-FDG PET-CT	Further imaging, biopsy, clinical follow-up	Added information from ^{18}F-FDG PET-CT
1	localized	US/XR/CT/MRI /BS	3.0	no	–	no
2	localized	US /XR /CT /MRI /BS	2.2	no	–	no
3	metastatic	US /XR /CT	8.1	FDG positive lesion	CT confirm metastases	yes (true positive lesion)
4	localized	US /XR /CT /MRI /BS	20.8	no	–	no
5	localized	US /XR /CT /MRI /BS	7.2	FDG positive lesions	biopsy –benign histology	no (false positive lesions)
6	metastatic	US /XR /CT /MRI	17.0	no	–	no
7	localized	US /XR /CT /MRI /BS	3.8	FDG positive lesion	MRI and biopsy – benign histology	no (false positive lesion)
8	localized	US /XR /CT /MRI /BS	3.5	no	–	no
9	localized	US /XR /CT/ MRI	6.0	FDG positive lesion	clinical follow up – no development of metastases	no (false positive lesion)
10	localized	US /XR /CT /MRI /BS	7.0	no	–	no
11	metastatic	XR /CT /MRI /BS	4.0	no	–	no
12	metastatic	XR /CT /WB-MRI /BS	–	skeletal metastases on WB MRI, none on PET-CT or bone scan	–	no (false negative study)
13	metastatic	XR /CT /MRI /BS	4.4	FDG positive lesion	MRI confirm metastases	yes (true positive lesion)
14	localized	CT /MRI /BS	11.5	no	–	no
15	metastatic	US /XR /CT /MRI /BS	–	FDG positive lesion	clinical follow up - rapid progression of disease	yes (true positive lesion)
16	metastatic	XR /CT /MRI	–	FDG positive lesion	MRI confirm metastases	yes (true positive lesion)
17	metastatic	XR /CT /MRI / BS	4.3	no	–	no
18	localized	XR /CT / MRI /BS	12.6	no	–	no
19	localized	XR /CT /MRI /BS	–	no	–	no

SUV_{max} maximum standardized uptake value; *US* Ultrasound; *XR* radiography/X ray; *CT* Computed Tomography; *MRI* Magnetic Resonance Imaging; *WB-MRI* Whole Body Magnetic Resonance Imaging; *BS* bone scan; ^{18}F-FDG PET-CT ^{18}F Fluorodeoxyglucose Positron Emission Tomography Computed Tomography

more metastases than conventional imaging in 21% of the patients. This did not; however, upstage any of the patients as they all had extensive metastatic disease shown by conventional imaging and no changes in planned treatment was made. In one patient the ^{18}F-FDG PET-CT study was false negative. ^{18}F-FDG PET-CT showed false positive lesions in three patients. The estimated cumulative mean effective radiation dose

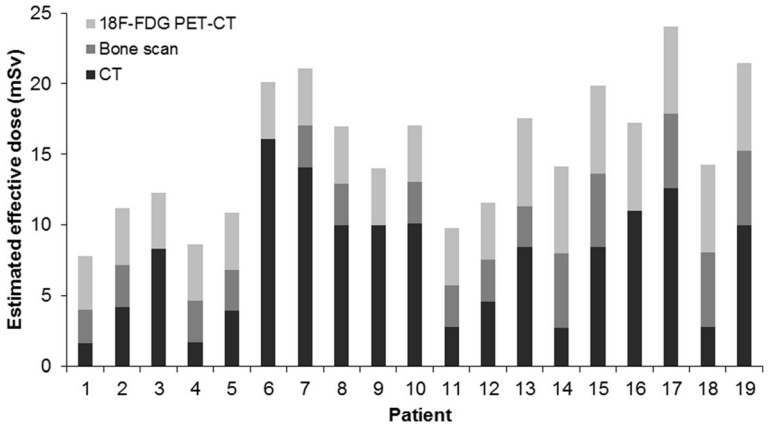

Fig. 2 Estimated effective patient dose (mSv) from bone scan, CT and ^{18}F-FDG PET-CT examinations performed for staging, in each of the 19 patients in the cohort

received from imaging at staging was 15 mSv. ^{18}F-FDG PET-CT contributed in mean to 1/3 (33%) of the received radiation dose.

Several imaging methods exist for staging patients with Ewing sarcoma and there is a need for optimisation of imaging strategies. One of the objectives of the ongoing multicentre study Euro Ewing 2008 (Group EES, 2010) is to determine the value of ^{18}F-FDG PET-CT for diagnosis and treatment evaluation in these patients. In the Euro Ewing study protocol ^{18}F-FDG PET-CT (if available at the treating institution) should be performed three times: at staging, at early response assessment and at late response assessment. Few studies have compared ^{18}F-FDG PET-CT and conventional imaging in patients with Ewing sarcoma (Quartuccio et al., 2015; Fuglo et al., 2012). In a study of 89 patients with high-grade bone- and soft tissue sarcomas (11 with Ewing sarcoma) by Fuglø et al., ^{18}F-FDG PET-CT had a high sensitivity of 95%, and specificity of 96% for detecting distant metastases (Fuglo et al., 2012). In a study of 44 patients with Ewing sarcoma, Quartuccio et al. found that ^{18}F-FDG PET-CT had superior performance on follow-up than for initial staging (accuracy 85% versus 69%) (Quartuccio et al., 2015). ^{18}F-FDG PET-CT detected more metastatic lesions in nine patients (21%) and characterized suspected lesions more accurately in twelve patients (27%). Their analyses showed that ^{18}F-FDG PET-CT performed similar to MRI in detecting skeletal metastases. In a retrospective study of 53 patients with skeletal Ewing sarcoma, Sharma et al. found that ^{18}F-FDG PET-CT had a high accuracy (92%) for detecting recurrence in patients with primary Ewing sarcoma (Sharma et al., 2013). However, the authors admitted that lack of histopathological confirmation of all metastases and lack of data from conventional imaging might have led to a falsely high sensitivity for ^{18}F-FDG PET-CT.

In one patient with multiple skeletal metastases, the ^{18}F-FDG PET-CT study was found to be false negative. The skeletal metastases were easily detectable on whole body MRI while no increased uptake of radioactive tracer in the skeleton were seen in the ^{18}F-FDG PET-CT study or the skeletal scintigraphy images. Without performing whole body MRI in this patient, the skeletal metastases might have been missed.

In three patients with local disease the ^{18}F-FDG PET-CT studies showed false positive findings. In one patient ^{18}F-FDG PET-CT showed a focal FDG uptake in muscle that subsequent biopsy proved to be benign. In two other patients ^{18}F-FDG PET-CT showed

slightly increased FDG uptake in lymph nodes but excisional biopsy and clinical follow-up revealed these to be reactive lymph nodes. FDG uptake in reactive lymph nodes is a well-known confounder in ^{18}F-FDG PET-CT studies in all tumour entities, as there is increased ^{18}F-FDG accumulation in inflammatory cells. In their study of 89 patients with bone sarcomas and soft tissue tumours, Fuglø et al. found that the positive predictive value of ^{18}F-FDG PET-CT for detection of lymph node metastases was only 27% (all tumours combined) (Fuglo et al., 2012). The negative predictive value was, however 100%. The three false positive ^{18}F-FDG PET-CT findings in our study could have led to an upstaging of the patients disease if supplementing biopsy and imaging had not ruled out metastases. This highlights the importance of performing supplementary imaging or biopsy of suspected FDG positive metastases.

Altogether ^{18}F-FDG PET-CT detected more metastases than conventional imaging in four of our study patients. In two of the patients ^{18}F-FDG PET-CT detected a FDG positive lesion in an internal organ. Clinical follow-up and MRI confirmed metastatic disease. In two other patients ^{18}F-FDG PET-CT detected additional skeletal metastases that were confirmed by subsequent MRI and CT. Both these patients however, lacked a skeletal scintigraphy at staging and most probably, the FDG positive skeletal lesions would have been detected in a skeletal scintigraphy. The detection of skeletal lesions with ^{99m} Tc skeletal scintigraphy is based upon accumulation and binding of ^{99m} Tc-methylene diphosphonate (MDP) or ^{99m} Tc- hydroxymethylene diphosphonate (HDP) on hydroxyapatite crystals in areas of bone with increased osteoblastic activity. Osteosclerotic lesions with high ostoblastic activity are therefore more easily detected in skeletal scintigraphy than pure osteolytic lesions. Ulaner et al. (Ulaner et al., 2014) did a retrospective review of pre therapeutic MDP skeletal scintigraphy and ^{18}F-FDG PET-CT examination in 60 patients with Ewing sarcoma (12 had skeletal metastases). They found that the MDP skeletal scintigraphy did not add any new information when the primary tumour was osteolytic. When the primary tumour was osteosclerotic however, the MDP skeletal scintigraphy was more sensitive than ^{18}F-FDG PET-CT in detecting osseous metastases. In a retrospective study of 91 patients with Ewing sarcoma with pre therapeutic skeletal scintigraphy and ^{18}F-FDG PET (not combined with CT), Newman et al., found that ^{18}F-FDG PET was slightly superior to skeletal scintigraphy in screening for skeletal metastases (Newman et al., 2013). The skeletal scintigraphies had however, a higher sensitivity for detection of skeletal lesions in the skull due to increased FDG uptake in brain obscuring nearby focal FDG uptake in the skull in the ^{18}F-FDG PET-CT images. We observed full concordance regarding skeletal lesions between skeletal scintigraphy and ^{18}F-FDG PET-CT in the fourteen patients having both examinations.

One of the strengths of our study is that we have only included patients with histopathological proven tumours belonging to the Ewing sarcoma family of tumours (Murphey et al., 2013). Other studies evaluating ^{18}F-FDG PET-CT and Ewing sarcoma have a mixed population of patients with other bone sarcomas, soft tissue sarcomas and Ewing sarcoma (Quartuccio et al., 2015; Fuglo et al., 2012; Sharma et al., 2013). Our study is a population-based national retrospective study of all patients below 30 years of age diagnosed with Ewing sarcoma between January 1st 2005 and December 31st 2012 and all patients have been treated according to the national guidelines of Ewing sarcoma (Helsedirektoratet Avdeling sykehustjenester Oslo Norway, 2015). We

have a very comprehensive set of comparable conventional imaging on all the patients and we have complete medical data including radiological, nuclear medicine and pathology reports on all patients, for a minimum follow-up of 12 months.

Quartuccio et al. (Quartuccio et al., 2015) found changes in management that could be linked to the added information from the ^{18}F-FDG PET-CT studies in nine of the 64 patients (14%). As discussed in their study it is hard to evaluate the effects of imaging findings on patient management in a retrospective study since treatment decisions are taken by physicians influenced by many additional factors other than imaging findings, and the treatment decision is not always well documented. In our patient cohort, pre therapeutic ^{18}F-FDG PET-CT gave additional information compared to conventional imaging in four of the patients in our study (4 of 19). The added information had, however, no impact on the planned treatment in any of these patients as they all had extensive metastatic disease at time of diagnosis. The increased amount of radiation from ^{18}F-FDG PET-CT of 33% of the total radiation dose from all staging examinations seems justifiable regarding the usefulness of the added information.

The present study has some limitations. Ewing sarcoma is a rare disease and in order to collect enough patients retrospective studies are usually applied. Our patient cohort is too small to perform any calculations regarding accuracy of the method ^{18}F-FDG PET-CT in staging of Ewing sarcoma patients. However, the study provides an insight of how useful the method has been in evaluating disease burden in the 19 patients in our cohort during the period 2005 to 2012. As the study is a retrospective quality-control study, we did not have consent to re-evaluate the images. We have compared the radiological and nuclear medicine reports given by the various radiologists and nuclear medicine specialists at the time of diagnosis. The reporting specialists not only base their reports on the present examinations but also take into account all available examinations and are not "blinded" to the results from prior imaging of the patient. Our study describe the "real life" scenario where all information from existing studies are considered together when staging a patient and not a "study design" scenario where the ^{18}F-FDG PET-CT studies are read by specialists "blinded" from the results from conventional imaging. When estimating the total effective radiation dose the patients receives during staging, we chose to leave out all radiation doses from planar radiography. In a previous study we have conducted on radiation doses in patients with Ewing sarcoma, we found that the estimated effective doses of all the planar radiography examinations during staging and treatment contributed to only 7% of the total estimated radiation doses from all nuclear and radiological imaging (Johnsen et al., 2016). We estimate that the planar radiography examinations performed during staging contributed to less than 7% and therefore chose to omit these examinations in our estimation.

Conclusion

Pre therapeutic ^{18}F-FDG PET-CT of patients with Ewing sarcoma improves detection of metastases compared to conventional imaging. False FDG positive lesions are quite common and supplementary imaging or biopsies are often necessary. Radiation dose from the ^{18}F-FDG PET-CT examination amount to 1/3 of the total estimated cumulative mean radiation dose received by the patients from other imaging modalities during staging of their disease.

Abbreviations
18F: Fluorine-18; 99 m Tc: Technetium-99 m; BS: Bone scan; CT: Computed tomography; DTPA: Diethylenetriaminepentaacetic acid; EANM: European association of nuclear medicine; ES: Ewing sarcoma; EWSR1: Ewing sarcoma breakpoint region 1; FDG: Fluorodeoxyglucose; GFR: Glomerular filtration rate; HDP: Hydroxymethylene diphosphonate; ICRP: International commission on radiation protection; ISG: Italian sarcoma group; LDH: Lactate dehydrogenase; MDP: Methylene diphosphonate; MRI: Magnetic resonance imaging; PET: Positron emission tomography; PET-CT: Positron emission tomography –computed tomography; RNA: Ribonucleic acid; SSG: Scandinavian sarcoma group; SUV max: Maximum standardized uptake value; SUV: Standardized uptake value; Sv: Sievert; US: Ultrasound; XR: Planar radiography

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Availability of data and materials
Not applicable

Authors' contributions
The authors have all provided substantial contributions in analysing and interpretating study data, in revising the manuscript and have all given their approval of the final version of the manuscript.

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
Informed consent for registration in the National Sarcoma Register at Oslo University Hospital was obtained from all individual participants included in the study. The study was approved as a quality-control study by the Regional Medical Ethics Committee of Western Norway and the local Data Protection officer.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

Publisher's Note

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