Retrospective analysis of use of fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) for detection of metastatic lymph nodes in dogs diagnosed with appendicular osteosarcoma

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Abstract

The purpose of this retrospective analysis was to determine if fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}F-FDG PET/CT) could potentially be an accurate staging tool for detecting metastatic lymph nodes in dogs with appendicular osteosarcoma based on the quantitative measurement of the maximum standard uptake value (SUV_{max}) of lymph nodes. A total of 53 dogs were identified that presented for staging *via* ^{18}F-FDG PET/CT for primary appendicular osteosarcoma. Patients were categorized according to lymph node status of having either metastatic or non-metastatic nodes based on cytological or histological analysis. Maximum standard uptake (SUV_{max}) values of the sampled lymph node(s) were recorded and 3/77 (3.9%) of sampled lymph nodes were confirmed metastatic. A Mann-Whitney test revealed a statistical difference in the SUV_{max} of the metastatic *versus* non-metastatic lymph nodes [median: 6.6 to 95% confidence interval (CI): 2.56 to 14.37 *versus* 2.18 95% CI: 2.32 to 3.17, respectively, *P*-value = 0.05]. This retrospective analysis revealed a significant difference in the SUV_{max} as measured on ^{18}F-FDG PET/CT between metastatic lymph nodes and non-metastatic lymph nodes in canine patients afflicted with appendicular osteosarcoma, in spite of the small numbers analyzed. While these results are promising, they should be interpreted with caution and further studies are justified.

Résumé

Le but de cette analyse rétrospective était de déterminer si la tomographie par émission de positons avec le fluor-18 fluorodésoxyglucose/tomodensitométrie (^{18}F-FDG TEP/CT) pourrait potentiellement être un outil de stadification précis pour la détection des ganglions lymphatiques métastatiques chez les chiens atteints d'ostéosarcome appendiculaire basé sur la quantification de la valeur standard maximale d'absorption (SUV_{max}) des ganglions lymphatiques. Les auteurs ont identifié 53 chiens qui furent classifiés avec le ^{18}F-FDG TEP/CT pour l'ostéosarcome appendiculaire primaire. Les patients ont été classés, selon l'état des ganglions lymphatiques, à avoir des ganglions métastatiques ou non métastatiques sur la base d'une analyse cytologique ou histologique. Les valeurs d'absorption standard maximale (SUV_{max}) du ou des ganglions lymphatiques échantillonnés ont été enregistrées et 3/77 (3,9 %) des ganglions lymphatiques échantillonnés ont été confirmés métastatiques. Un test de Mann-Whitney a révélé une différence statistique du SUV_{max} des ganglions lymphatiques métastatiques versus *non métastatiques [médiane : 6,6 à 95 % intervalle de confiance (IC) : 2,56 à 14,37* versus *2,18 IC à 95 % : 2,32 à 3,17, respectivement, valeur de* P *= 0,05]. Cette analyse rétrospective a révélé une différence significative dans le SUV_{max} tel que mesuré sur ^{18}F-FDG TEP/CT entre les ganglions lymphatiques métastatiques et les ganglions lymphatiques non métastatiques chez les patients canins atteints d'ostéosarcome appendiculaire, malgré le petit nombre analysé. Bien que ces résultats soient prometteurs, ils doivent être interprétés avec prudence et des études complémentaires sont justifiées.*

(Traduit par Docteur Serge Messier)

Introduction

Osteosarcoma (OSA) is the most prevalent osseous neoplasm affecting dogs (1). Osteosarcoma can affect both the axial and appendicular skeleton, as well as extra-skeletal tissues. The most common sites of metastasis are the lungs and skeletal tissues (1). The metastatic rate of OSA to the locoregional lymph nodes has been shown to be low in both canines and humans: roughly 4.4% in canines (2) and 10.4% in humans (3).

Staging of patients with appendicular OSA traditionally involves a combination of procedures, including complete blood (cell) count (CBC) and chemistry, radiographs of the affected site, and 3-view

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thoracic radiographs as a standard of care. Additionally, whole-body computed tomography (CT) imaging, abdominal ultrasound, nuclear scintigraphy, and cytology/histopathology of locoregional lymph nodes can all be potentially recommended (4). Staging of patients with osteosarcoma is important in determining a prognosis, as it allows the client to make an informed decision about therapy. Prognosis for canine patients diagnosed with osteosarcoma depends on many factors, including but not limited to, tumor size, tumor metastasis, monocyte count, primary tumor location, and serum alkaline phosphatase (2,5–12).

Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is an imaging modality that combines functional and anatomical imaging with use of a radioactive pharmaceutical and 3D reconstruction of the anatomical images. Fluorodeoxyglucose (FDG) is a glucose analog that is taken up by metabolically active cells, such as inflammatory cells and cancer cells. Some regions in the body, including the heart, salivary glands, and brain, exhibit increased uptake of FDG as a normal variant (13).

Quantitative analysis of the positron emission tomography/computed tomography (PET/CT) images allows the user to objectively measure the degree of uptake of the ^{18}F-FDG *via* a number known as a standard uptake value (SUV). The most commonly reported value is the maximum standard uptake value (SUV_{max}). Tissues that have a higher uptake of a radionuclide are referred to as having a higher avidity (14). A recent study in dogs afflicted with appendicular OSA showed that quantitative measurement of SUV_{max} of the primary tumor was prognostic for survival, with an increasing SUV_{max} value of the lesion significantly associated with an increased risk of death (15).

The presence of lymph node metastasis is one of the well-documented negative prognostic factors for dogs afflicted with appendicular osteosarcoma (2). Median survival time (MST) for dogs with appendicular osteosarcoma treated with the standard of care, which involves removing the primary tumor and chemotherapy, ranges from 9 to 17 mo (1). If metastasis to the local lymph nodes is present at the time of diagnosis, this MST falls precipitously to a median of 59 d (2). The ability to detect metastatic lymph nodes is therefore extremely important in establishing the prognosis and appropriate treatment decisions for these patients. The accurate detection of lymph node metastasis can often be very difficult on imaging studies. This has been shown to be true for CT imaging in general, as there is a moderate amount of overlap in the CT characteristics of normal, reactive, and metastatic lymph nodes (16).

The purpose of this retrospective analysis was to determine if ^{18}F-FDG PET/CT could potentially be an accurate staging tool in detecting metastatic lymph nodes in dogs with appendicular osteosarcoma based on the quantitative measurement of the SUV_{max} of lymph nodes.

Materials and methods

A retrospective search of medical records was carried out at the Colorado State University — Veterinary Teaching Hospital (CSU-VTH). Dogs included in this study were from a population of privately owned pets that presented to the CSU-VTH from December 1, 2009 to May 8, 2019 for staging of a known or presumed primary appendicular osteosarcoma (based on clinical history, CT characteristics, and cytology or histopathology). Patients were included in the study if they had cytological or histological sampling of lymph node(s) after ^{18}F-FDG PET/CT scan.

Patients were categorized based on lymph node status of having either metastatic or non-metastatic nodes based on cytological or histological analysis done by Board-certified veterinary pathologists. Maximum standard uptake (SUV_{max}) values of the sampled lymph node(s) were recorded and each lymph node was treated as an independent variable. Patients were included in this study in accordance with appropriate Institutional Care and Use Committee or Clinical Review Board protocols, permissions, or exemptions. Final determination of the appropriateness of inclusion of a patient in this study was based on consensus review by the authors.

Dogs were fasted for a minimum of 6 h before PET/CT. Prior to anesthesia, a blood glucose level was taken and dogs were not scanned if they were hyperglycemic (normal range: 70 to 115 mg/dL). Dogs underwent ^{18}F-FDG PET/CT imaging with a Philips Gemini TF Big Bore 16-slice PET/CT scanner (Philips North America, Andover, Massachusetts, USA), under general anesthesia according to a protocol described in a previous study (17). Anesthetic protocol was approved by a Board-certified veterinary anesthesiologist and generally consisted of an opioid premedication, induction with propofol (PropoFlo; Abbott Labs, North Chicago, Illinois, USA), and maintenance with inhalant gas (IsoFlo; Abbott Labs). Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) (Cardinal Health, Dublin, Ohio, USA) was injected intravenously at a dose of 5.18 to 6.29 MBq (0.14 to 0.17 mCi) per kilogram body weight (BW) and the patient was positioned in dorsal recumbency.

After a 1-hour uptake period, a whole-body CT scan (pre- and post-contrast) was obtained for anatomic correlation and attenuation correction. Acquisition parameters were: 120 kV, 100 mAs/slice, 0.75 s rotation time, 0.813 pitch, matrix 768 × 768, field of view (FOV) 600 mm, and 0.75 to 1.5 mm (dependent on patient size) × 16 detector width. A dose of 350 mg I/mL iohexol (Omnipaque 350; GE Healthcare, Princeton, New Jersey, USA) was given intravenously *via* power injector (Medrad Stellant dual head power injector) at a dose of 2 mL/kg BW (700 mg I/kg). Immediately following the post-contrast CT, a whole-body PET scan was obtained and CT attenuation-corrected (CTACs) images and non-attenuation-corrected (NAC) images of the PET were reconstructed.

Images were assessed retrospectively by 2 Board-certified radiologists (LG and ER), radiology residents, and the primary author using IntelliSpace Portal radiology DICOM image-processing application software (Version 8; Philips Medical System, Eindhoven, The Netherlands). Regions of interest (ROIs) were placed over all lymph nodes that had available cytology. The ROI was expanded in a 3-dimensional fashion to include the entire lymph node and the standard uptake value maximum (SUV_{max}) was recorded, as shown in Figure 1.

Data were analyzed using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California, USA). Lymph nodes were categorized as metastatic or non-metastatic, based on cytology and histopathology reports. The data were determined to be non-normally distributed using a Shapiro-Wilk test. Descriptive statistics were generated for all lymph nodes, metastatic lymph

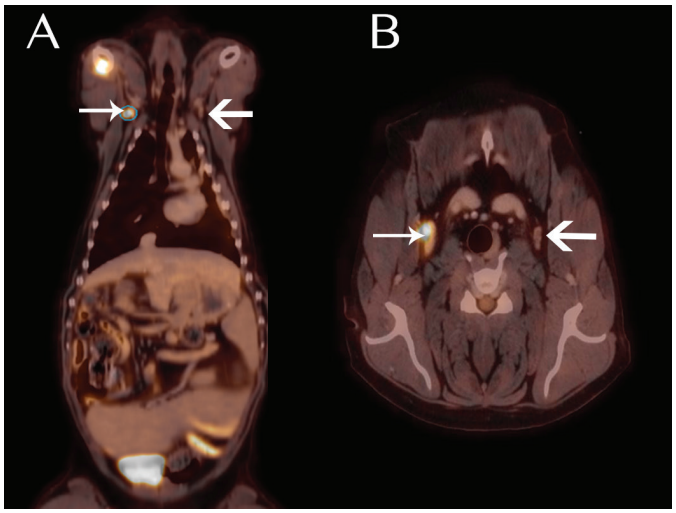

Figure 1. Representative images of patient in the dorsal and transverse plane with a primary appendicular right humeral osteosarcoma. Note the metastatic right axillary lymph (thin arrow) and non-metastatic contralateral left axillary lymph node (thick arrow).

Table I. Descriptive statistics.

	All lymph nodes	Metastatic lymph nodes	Non-metastatic lymph nodes
N	77	3	74
Mean	2.87	5.9	2.75
Median	2.2	6.6	2.18
Mode	2.2	N/A	2.3
Standard error	0.22	1.97	0.21
Standard deviation	1.97	3.41	1.83
Sample variance	3.88	11.62	3.33
Kurtosis	4.16	N/A	5.69
Skewness	1.82	−0.88	1.96
Range	10.87	6.71	10.87
Minimum	0.48	2.2	0.48
Maximum	11.35	8.91	11.35
Confidence level (95%)	0.45	8.47	0.43
Lower	2.42	−2.56	2.32
Higher	3.32	14.37	3.17

nodes, and non-metastatic lymph nodes (Table I). Statistical analysis was carried out comparing the SUV_{max} values of metastatic lymph nodes to non-metastatic lymph nodes. Due to the small sample size of the metastatic lymph nodes and non-normally distributed data, a Mann-Whitney U-test was chosen as the appropriate statistical test. A scatter plot of the data points, as well as depiction of the median, was generated, as shown in Figure 2.

Results

A total of 114 patients was initially identified as having been staged for primary appendicular osteosarcoma using ^{18}F-FDG PET/CT and 54 of these patients met the inclusion criteria of lymph node sampling after imaging. Of these 54 patients, 1 patient was removed from analysis due to a data transfer error that made it impossible to quantitatively analyze the ^{18}F-FDG PET/CT. Of the remaining 54 patients, 77 lymph nodes were sampled, including 15 popliteal, 3 medial iliac, 29 axillary, and 30 superficial cervical.

The median age of the dogs was 8.2 y (range: 1.2 to 13.3 y). There were 23 castrated males, 26 spayed females, 4 intact males, and 0 intact females. Twenty different breeds were represented in the subject population, including 10 mixed breeds, 8 golden retrievers, 7 Labrador retrievers, 3 Rottweilers, 3 Staffordshire terriers, 3 mastiffs, and 3 Saint Bernards. The remaining 16 dogs consisted of 13 other different breeds. Primary tumor sites included 22 distal radii, 13 proximal humeri, 7 distal femurs, 5 distal tibias, 3 proximal tibias, 2 distal ulnas, 1 proximal ulnas, and 1 metatarsus II.

Of the 77 lymph nodes with diagnostic sampling, 22 were sampled *via* cytology, 49 were sampled *via* histopathology, and 6 were sampled by both cytology and histopathology. Multiple lymph nodes were sampled in approximately 23 patients. The lymph nodes selected for sampling were based on them being the locoregional lymph node in relation to the primary tumor location and/or based on the lymph node PET/CT imaging characteristics (abnormal size, abnormal shape, reactivity of surrounding tissues, increased avidity). The 6 lymph nodes that were sampled with both cytology and histopathology were determined by the veterinary pathologist to be inconclusive cytological samples, which then warranted their sampling for histopathology. A total of 3/77 (3.9%) lymph nodes were confirmed as metastatic, all *via* histopathology.

The median SUV_{max} of the lymph nodes (n = 77) was 2.2 (range: 0.48 to 11.35) and the non-metastatic lymph nodes (n = 74) was 2.18 (range: 0.48 to 11.35). The median SUV_{max} of the metastatic lymph nodes (n = 3) was 6.6 (range: 2.2 to 8.91). The difference between metastatic and non-metastatic lymph nodes was evaluated with a Mann-Whitney U-test and reported to be statistically significant (P-value = 0.05).

Discussion

This retrospective study suggests that ^{18}F-FDG PET/CT could be a valuable tool in detecting metastatic lymph nodes in dogs diagnosed with appendicular osteosarcoma based on the measurement of maximum standard uptake (SUV_{max}) values. Despite the small number of metastatic lymph nodes, a significant difference in SUV_{max} was measured between metastatic and non-metastatic lymph nodes. Although the results of the Mann-Whitney test calculated a significant P-value, the results should be interpreted with caution given the low sample size of metastatic lymph nodes.

The lymph node status is one of the most important prognostic indicators of poor survival for almost all malignant solid tumors. Eight editions of the Union for International Cancer Control's (UICC) Tumor, Nodes, and Metastases (TNM) rules of classification and staging have been published, all of which emphasize that nodal involvement in cancer significantly influences prognosis and therapeutic decision-making (18,19). In most cancers, both the disease-free interval (DFI) and the median survival time (MST) are significantly greater for patients that do not have metastatic disease to the lymph nodes. Hillers et al (2) reported the median DFI as 238 d and the median MST as 318 d for dogs with appendicular OSA

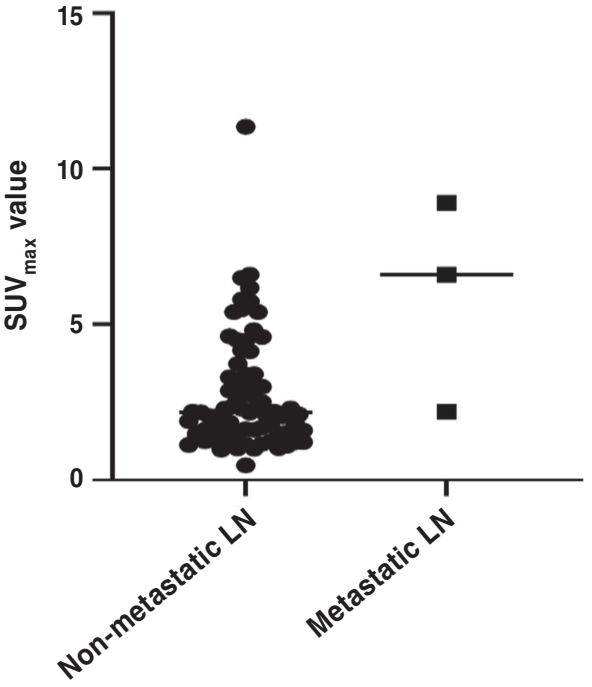

Figure 2. Scatter plot comparison of SUV_{max} values of non-metastatic (median: 2.18, range: 0.48 to 11.35) to metastatic lymph nodes (LN) (median: 6.6, range: 2.2 to 8.91) (*P*-value 0.05).

without metastasis to the lymph nodes compared to a median DFI of 48 d and a median MST of 59 d for dogs that do have metastasis to the lymph nodes.

A recent meta-analysis of 26 studies concluded that ^{18}F-FDG PET/CT had a 90 to 100% success rate in the diagnosis, staging, and reoccurrence monitoring in human patients diagnosed with osteosarcoma (20). This meta-analysis also determined that there was a 90% sensitivity and 96% specificity for detection of metastatic lesions at distant sites, including lymph nodes (20). Multiple studies in human medicine have indicated that ^{18}F-FDG PET/CT identification of metastatic lymph nodes in multiple cancer types is highly sensitive and specific (21–25). Song et al (26) reported that the lymph node SUV_{max} on pre-operative ^{18}F-FDG PET/CT is a significant independent predictor of both recurrence-free survival and overall survival after curative resection in gastric cancer patients. Additionally, quantitative evaluation of ^{18}F-FDG PET/CT scans on not only the primary tumor but also on lymph node and distant metastasis in humans with biliary tract cancer have also been linked to survival as detection of disease will alter the management of the patients (27).

Although ^{18}F-FDG PET/CT appears to be significantly useful for detecting metastatic lymph nodes, there is still the risk of false positives and false negatives. Because FDG is taken up by metabolically active cells, areas of inflammation may also have an elevated SUV_{max} (28). Locoregional lymph nodes of a diseased patient can be either normal, reactive, or metastatic, with the SUV_{max} ranges often overlapping. Thus, if a locoregional lymph node is highly reactive, based solely on its SUV_{max} value, we can create a false-positive diagnosis of a metastatic lymph node. Alternatively, Purohit et al (29) reported that a lymph node can be so necrotic that there is not enough metabolically active tissue to take up the FDG, which creates a false negative interpretation.

A limitation of this retrospective study was that 22/77 lymph nodes were diagnosed as metastatic or non-metastatic based on cytology. In different studies, both Langenbach et al (30) and Ku et al (31) state that cytology is an accurate tool for detecting metastatic spread to the lymph nodes. Both these studies compared cytological results to histological results. Langenbach et al (30) conducted a well-controlled prospective study citing that cytology has a sensitivity of 100% and a specificity of 96% for detecting metastatic neoplasia. Ku et al (31) carried out a retrospective study, including lymph node samples from 296 dogs, and reported a 90% specificity, 73% sensitivity, and 80% accuracy for detecting metastatic nodes with cytological examination. There are inherent risks of false negative cytological results due to sampling error, poor sample exfoliation, and differences in interpretation among pathologists. Histopathology therefore remains the gold standard for definitive tissue/cellular identification. No metastatic lymph nodes were detected with cytology in this study population.

Another limitation of this study was the small number of sampled lymph nodes compared to the number of patients imaged. The primary reason patients did not have lymph nodes sampled after ^{18}F-FDG PET/CT was patient or client constraints. The 3.9% metastatic nodes identified out of all lymph nodes sampled is on par with other reported metastatic rates to lymph nodes in patients with appendicular osteosarcoma (2). Although the sample size is low, the results are promising, and future studies should aim to have all local regional lymph nodes sampled prospectively to increase the power and improve the accuracy of the statistical analysis.

Another limitation of this study would be that in veterinary medicine access to PET/CT is primarily limited to university hospitals and research facilities. The clinical usefulness of this staging tool has yet to be fully exploited and it may eventually become more widespread, similar to in the early 2000s when it was considered unrealistic to use other forms of advanced imaging such as MRIs as a common staging tool (32). At this time, investigating the sensitivity of ^{18}F-FDG PET/CT for diagnosing metastatic disease for a variety of naturally occurring tumors in dogs is a valuable research endeavor. Methods used in this study can be adapted to future studies to explore other tumor types and the SUV_{max} values of locoregional lymph nodes.

An SUV_{max} cutoff value for determining metastatic *versus* non-metastatic lymph nodes in dogs with appendicular OSA cannot be determined at this time. Some studies in human types of cancer have used various types of analysis to establish significant SUV_{max} cutoff values for lymph node metastasis (21–23,33–35). It is the commonly held view, however, that SUV_{max} values tend to be non-transferable among institutions due to differences in image-acquisition parameters, timing, protocols, software, and imaging equipment (36).

This retrospective analysis revealed a significant difference in the SUV_{max} as measured on ^{18}F-FDG PET/CT between metastatic lymph nodes and non-metastatic lymph nodes in canine patients afflicted with appendicular osteosarcoma in spite of the small sample size. When staging patients with this type of tumor, it would therefore be worth considering having lymph nodes cytologically or histologically evaluated when the node shows increased avidity on its scan.

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