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Clinical science

FDG-PET/CT discriminates between patients with and without lymphomas in primary Sjögren's syndrome

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Abstract

Objectives: To assess the usefulness of [^{18}F]-fluorodeoxyglucose (FDG)-PET/CT (i) to discriminate between primary SS (pSS) patients with and without lymphomas and (ii) to evaluate systemic disease activity in pSS.

Methods: ACR-EULAR-positive pSS patients who underwent FDG-PET/CT were included. Scans were visually evaluated and quantitative analysis was performed by measuring standardized uptake values (SUV) of salivary and lacrimal glands and systemic regions. Receiver operating characteristic curve analyses were performed to find SUV cut-off values to discriminate between lymphoma and non-lymphoma.

Results: Of the 70 included patients, 26 were diagnosed with a pSS-associated lymphoma, mostly of the mucosa-associated lymphoid tissue type (23/26). Lymphoma patients showed higher FDG uptake in the parotid and submandibular glands, and more frequently showed presence of nodular lung lesions, compared with non-lymphoma patients. The accuracy of the maximum SUV (SUVmax) in the parotid and submandibular gland to predict lymphoma diagnosis was good, with optimal cut-off points of 3.1 and 2.9. After combining these three visual and quantitative findings (nodular lung lesions, parotid SUVmax $>$ 3.1 and submandibular SUVmax $>$ 2.9), sensitivity was 92% when at least one of the three features were present, and specificity was 91% in case at least two features were present. Furthermore, FDG-PET/CT was able to detect systemic manifestations in pSS patients, mostly involving lymph nodes, entheses and lungs.

Conclusions: FDG-PET/CT can assist in excluding pSS-associated lymphomas in patients without PET abnormalities, possibly leading to a decrease of invasive biopsies in suspected lymphoma patients. Furthermore, FDG-PET/CT is able to detect systemic manifestations in pSS and can guide to the best biopsy location.

Keywords: primary SS, FDG-PET/CT, imaging, lymphoma, salivary gland

Rheumatology key messages

- [^{18}F]-fluorodeoxyglucose (FDG)-PET/CT is useful in primary SS (pSS) patients suspected of high disease activity and/or a lymphoma.
- In pSS patients without PET abnormalities, FDG-PET/CT assists in excluding a pSS-associated lymphoma.
- FDG-PET/CT visualizes systemic manifestations in pSS and can guide to the best biopsy location.

Introduction

Primary SS (pSS) is characterized by symptoms of dry eyes, dry mouth and fatigue. Around 30–40% of pSS patients also suffer from systemic symptoms involving different organ systems, such as lungs, skin and nervous system [1–3]. A severe systemic complication of pSS is the development of a non-Hodgkin lymphoma, which occurs in around 5–10% of pSS patients and is mostly of the Mucosa Associated Lymphoid Tissue (MALT) type. These MALT lymphomas frequently develop in the parotid glands, but can also be found at other sites, such as submandibular and minor salivary glands, lacrimal glands, nasopharynx, lymph nodes, stomach and lungs [4, 5]. Although pSS-associated lymphomas usually have an indolent course, they are able to disseminate to other mucosal

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sites or organs, and around 10% of the low-grade pSS-associated lymphomas transform into high-grade lymphomas, mainly of the diffuse large B cell lymphoma (DLBCL) type [4, 6]. Furthermore, the 5- and 10-year overall survival of pSS patients with a MALT lymphoma was recently shown to be 91% and 79%, with a 10-year free event rate of only 45%, which also emphasizes the need for early detection and proper follow-up of pSS-associated lymphomas [7].

In clinical practice, differentiation between lymphoma and other systemic activity in pSS can be challenging, as clinical and serological findings associated with lymphoma can also be associated with systemic disease activity. Nowadays, a biopsy of the lymphoma-suspected location is the gold standard to diagnose a pSS-associated lymphoma. Imaging techniques could, however, assist in detection and staging of lymphomas by visualizing lymphoma locations throughout the body, and could aid in deciding the best biopsy location [8]. PET accompanied by a low-dose or contrast enhanced CT (PET/CT), which is based on injection of radiopharmaceuticals (tracers), is widely used in oncological and inflammatory diseases. The most used and widely available PET tracer is [^{18}F]-fluorodeoxyglucose (FDG). Metabolically active cells, such as tumour and inflammatory cells, show relatively high uptake of FDG. Although the usefulness of FDG-PET/CT is well recognized in high-grade lymphomas [8, 9], its role in pSS-associated MALT lymphomas is still controversial due to variable FDG avidity at different MALT locations [10, 11]. Despite the variability in FDG uptake in MALT lymphomas, previous studies reported that higher standardized uptake values (SUV), a quantitative method to measure FDG uptake at certain locations, in the salivary glands of pSS patients were associated with the presence of pSS-associated lymphomas [12]. Furthermore, irrespective of lymphoma diagnostics, the usefulness of FDG-PET/CT in detecting systemic disease activity in pSS was described [12–14]. However, these studies were relatively small, and different camera systems were used, without image reconstructions according to standardized European guidelines. So far, the SUVs are difficult to implement in clinical practice.

Therefore, the aim of this study was to assess the usefulness of FDG-PET/CT to: (i) discriminate between pSS patients with and without lymphomas, and (ii) evaluate systemic disease activity in daily clinical practice.

Methods

Patient selection

Patients fulfilling the ACR-EULAR criteria for pSS who underwent FDG-PET/CT were recruited from the electronic patient file system of the University Medical Center Groningen (UMCG). When patients were diagnosed as pSS before 2016, fulfilment of the ACR-EULAR criteria was assessed retrospectively [15]. Patients were excluded if standardized EANM Research Ltd (EARL) reconstructions were not available, if patients were scanned because of an intercurrent malignancy unrelated to pSS, in case of clinical diagnosis of another autoimmune disease and not pSS, or when the FDG-PET/CT scan was performed $\geq$1 month before pSS diagnosis. In cases where patients underwent multiple FDG-PET/CT scans, the first FDG-PET/CT scan was included. Ethical approval for this retrospective study was waived by the local medical ethics committee (METc2018/711). All patients were checked for objection against use of diagnostic data for research purposes in the electronic patient file system.

Retrieval of clinical data

Clinical data was retrieved from the electronic patient files, including age, disease duration, medication use and biopsy results performed to confirm or rule out a pSS-associated lymphoma, all around the time of FDG-PET/CT. The patients were divided into two groups. PSS patients with a histologically/cytologically proven lymphoma were included in the lymphoma group. The non-lymphoma group consisted of patients without lymphoma diagnosis who underwent a full clinical work-up, including biopsies of areas suspected of lymphoma, if indicated. Data of clinical examination, including EULAR SS DAI (ESSDAI) scores and serological results, were retrieved with a maximum time frame of 6 months from FDG-PET/CT. As the UMCG routinely performs parotid instead of labial gland biopsies in the work-up of pSS, parotid gland biopsy results performed during the diagnostic workup or follow-up of pSS were collected within a maximum time frame of 12 months from FDG-PET/CT.

FDG-PET/CT scanning

All FDG-PET/CT scans were performed on integrated PET/CT camera systems (Biograph mCT 40/64 or Vision, Siemens, Knoxville, TN, USA) and images were reconstructed according to standardized European EANM/EARL guidelines for quantification purposes [16]. According to the scanning protocol, patients were instructed to fast 6 h before 3 MBq FDG per kg body weight was injected i.v. [17]. PET/CT imaging started 60 min after FDG injection, and all patients were scanned from head to midthigh.

FDG-PET/CT analysis

FDG-PET/CT scans were visually and quantitatively analysed by two independent reviewers (A.W.J.M.G., M.S.G.), who were blinded for clinical data including the FDG-PET/CT report and all biopsy results, even when the indication of FDG-PET/CT was staging of a known (histologically diagnosed) lymphoma. Discrepancies were solved in a consensus discussion. For the salivary and lacrimal glands, visual assessment was rated from 0 to 3 (0: no uptake; 1: uptake = mediastinum, 2: mediastinum < uptake < liver; 3: uptake > liver; Fig. 1). Abnormal visual uptake was defined as: uptake $\geq$2 for the salivary glands and uptake $\geq$1 for the lacrimal glands, based on clinical expertise (A.W.J.M.G., M.S.G.). FDG-PET/CT images were visually evaluated for the presence systemic manifestations associated with pSS: uptake in lymph nodes (regions: head/neck, axillary, mediastinal, inguinal), arthritis, enthesitis, pulmonary abnormalities (inflammatory lesions, nodular lesions, interstitial lung disease), signs of nephritis, myositis, vasculitis, PMR or pancreatitis and thyroid abnormalities (thyroiditis, multinodular struma). Quantitative assessment was performed by measuring maximum (SUVmax), peak (SUVpeak) and mean (SUVmean) SUV within defined volumes of interest. Volumes of interest were drawn within the parotid and submandibular salivary glands and the lacrimal glands, and within the tonsils, thyroid gland, thoracic aorta (bloodpool), liver, spleen, pancreas, lung parenchyma and bone marrow. Diameters of salivary glands, liver and spleen were measured on the accompanying CT images. All assessments were performed using Syngo.Via VB40/50 software (Siemens Healthcare, Erlangen, Germany).

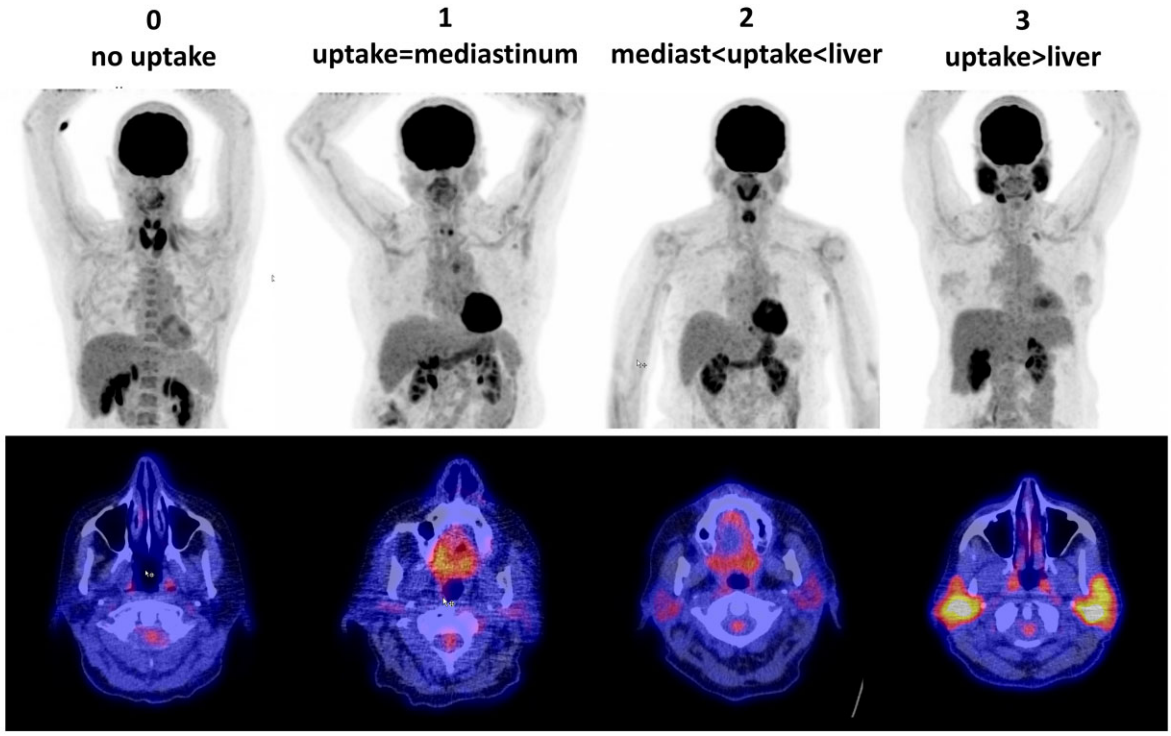

Figure 1. Visual analysis of FDG uptake in parotid salivary glands. Visual analysis based on scoring range 0–3, shown in PET images (upper row) and fused PET/CT-images of the same patients (lower row). Score 0: no FDG uptake in the glands; score 1: FDG uptake in the glands = FDG uptake in mediastinum; score 2: FDG uptake in the glands > FDG uptake in mediastinum, but < FDG uptake in the liver; score 3: FDG uptake in the glands > FDG uptake in the liver. FDG: [^{18}F]-fluorodeoxyglucose

Statistical analysis

Descriptive data were presented as mean (S.D.), median (interquartile range) or number (%) for normally and non-normally distributed continuous parameters or categorical parameters, respectively. Patient characteristics between pSS patients with and without lymphoma were compared using independent sample *T*-tests, Mann–Whitney *U* tests, χ^2 tests and Fisher's exact tests, as appropriate. The measured SUVs and diameters were compared between lymphoma-positive and lymphoma-negative patients using Mann–Whitney *U* tests. Differences in presence or absence of visual assessments was assessed using χ^2 tests and Fisher's exact tests. Associations between SUVs of the right and left salivary and lacrimal glands, and associations between clinical parameters and SUVs of the salivary glands were analysed using Spearman correlation coefficients and interpreted as poor association (0.0–0.2), fair (0.2–0.4), moderate (0.4–0.6), good (0.6–0.8) or excellent (0.8–1.0). Receiver operating characteristic curve analyses were performed to explore the accuracy of SUVs for both parotid and submandibular glands to predict the presence of lymphoma. Area under the curve (AUC) was interpreted as no discrimination (0–0.5), poor accuracy (0.5–0.7), fair (0.7–0.8), good (0.8–0.9) or excellent (0.9–1.0). The optimal cut-off point for SUVs was determined according to the highest Youden's index. All analyses were performed in IBM SPSS, version 28.

Results

Patients and biopsies

In total, 70 ACR-EULAR-positive pSS patients who underwent FDG-PET/CT were included. In most cases, FDG-PET/CT was performed because of high clinical disease activity of pSS/suspicion of a lymphoma (61%). Other indications were systemic staging of patients with a recently histologically diagnosed pSS-associated lymphoma (24%), suspicion of having an autoimmune disease (these patients had clinical signs of systemic disease activity/suspicion of a lymphoproliferative disorder and were retrospectively verified to have pSS at the time of FDG-PET) (7%) or an indication not related to any autoimmune disease (7%). Of the 70 included patients, 42 patients underwent biopsies of the suspected sites around the time of FDG-PET/CT. Biopsy sites were as follows: parotid gland ($N=23$), lacrimal gland/orbita ($N=3$), lungs ($N=3$), pleura/pleural fluid ($N=3$), lymph nodes ($N=7$), stomach/duodenum ($N=3$), bone marrow ($N=3$) and cavum nasi ($N=1$). In total, 26 patients were diagnosed with a lymphoma associated with pSS, mostly of the MALT lymphoma type, found in the parotid gland ($N=17$), lacrimal gland/orbita ($N=2$), lungs ($N=2$) and lymph nodes ($N=2$). The other three lymphoma patients were diagnosed with morbus Hodgkin, DLBCL in cavum nasi or a B cell lymphoma (biopsy site: mediastinal lymph node). All lymphoma patients underwent histological biopsies ($N=24$) or cytological punctions of lymph nodes ($N=2$), and all patients were extensively discussed in a multidisciplinary tumour board, with access to pathology, clinical and serological results. pSS patients with lymphomas ($N=26$) showed higher ESSDAI scores, higher RF levels and lower complement (C4) levels, compared with non-lymphoma patients ($N=44$). Differences in total ESSDAI scores were mostly caused by the lymphadenopathy and lymphoma domain. When the lymphoma item was not taken into account, ESSDAI scores were not significantly different between both patient groups (Table 1; Supplementary Fig. S1, available at *Rheumatology* online).

Table 1. Characteristics of patients included in retrospective FDG-PET/CT cohort

	pSS patients with pSS-associated lymphoma ($N = 26$)	pSS patients without lymphoma ($N = 44$)	*P*-value
Age at time of FDG-PET	58.6 (14.9)	57.3 (17.7)	0.758
Female	22 (84.6)	33 (75.0)	0.386
Disease duration at time of FDG-PET (years)	4.5 (0.0–9.5)	5.0 (1.0–11.8)	0.531
ACR-EULAR items			
Ocular item[a] (OSS $\geq$ 5 and/or Schirmer $\leq$ 5)	23 (95.8)	28 (77.8)	0.072
Oral item[a] (UWS $\leq$ 0.1 ml/min)	16 (84.2)	27 (75.0)	0.511
Serology item[b] (anti-SSA positivity)	22 (88.0)	37 (86.0)	1.000
Biopsy item[b] (positive labial and/or parotid gland biopsy)	26 (100)	40 (93.0)	0.285
ESSDAI scores[b]			
ESSDAI total score $\geq$5	26 (100)	29 (65.9)	**0.004**
ESSDAI score without lymphoma item	10.5 (5.5–14.3)	8.0 (4.0–16.0)	0.563
ESSDAI total score (with lymphoma item)	20.0 (16.0–23.3)	8.0 (4.0–16.0)	**<0.001**
Serology			
Haemoglobin levels (mmol/l)	7.7 (7.2–8.5)	7.5 (6.2–8.0)	0.085
Lymphocyte count (10^9/l)	1.23 (0.92–1.60)	1.42 (0.99–3.79)	0.055
ESR(mm/h)	27.5 (20.5–84.5)	69.0 (21.3–119.0)	0.065
IgG levels (g/l)	13.1 (10.2–18.1)	14.8 (12.3–24.1)	0.236
RF levels (IU/ml)	31.5 (9.6–164.0)	12.5 (2.5–42.3)	**0.029**
Complement C3 levels (g/l)	0.98 (0.92–1.21)	1.13 (0.97–1.34)	0.153
Complement C4 levels (g/l)	0.12 (0.04–0.17)	0.20 (0.14–0.25)	**0.005**
Presence of cryoglobulins[c]	11 (57.9)	12 (40.0)	0.221
Medication use at time of FDG-PET/CT			
Methylprednisone (1000 mg/day)[d]	0 (0)	2 (4.5)	0.526
Prednisone	1 (3.8)	6 (13.6)	0.246
Dosage of oral prednisone (mg/day)	5.0	10.0 (5.0–21.3)	
HCQ	6 (23.1)	5 (11.4)	0.193
Other immunosuppressant agents[e]	2 (7.7)	5 (11.4)	1.000

Data are presented as mean (S.D.), number (%) or median (interquartile range).
[a] Data are missing in 6–15 cases,
[b] data are missing in 1–2 cases,
[c] data are missing in 21 cases.
[d] Both patients were using methylprednisone <3 days at time of FDG-PET/CT.
[e] Abatacept, MTX, anakinra, AZA, SSZ. Bold text highlights significant values. FDG: [^{18}F]-fluorodeoxyglucose; pSS; primary SS; OSS: Ocular Staining Score; UWS: unstimulated whole saliva; ESSDAI: EULAR SS DAI.

Visual analysis—salivary and lacrimal glands

Abnormal visual FDG uptake (uptake $\geq$2) within the parotid and/or submandibular glands was found in 64% of the 70 included pSS patients. Patients with a pSS-associated lymphoma (at any location) more frequently showed FDG uptake $\geq$2 in the parotid and/or submandibular glands, compared with pSS patients without a lymphoma. Although only 10 pSS patients (14%) showed abnormal FDG uptake in the lacrimal glands (uptake $\geq$1), pSS patients with a lymphoma more frequently had FDG uptake $\geq$1, compared with non-lymphoma patients (Table 2).

Visual analysis—systemic manifestations

In almost all pSS patients (67/70, 96%) abnormal visual uptake was found in either the salivary glands and/or lymph node regions and/or a systemic region described in Table 2. Without taking the salivary glands and lymph nodes into account, 57% (40/70) of patients were positive for at least one visual systemic finding, with pulmonary abnormalities and enthesitis as the most frequent systemic FDG-PET/CT findings. Enthesitis was found in 31% (22/70) of pSS patients on FDG-PET/CT, mostly in the shoulder and hip regions. Interestingly, in some patients, signs of PMR, myositis, thyroiditis and arthritis/synovitis (shoulder, elbow, SI joint) were found on FDG-PET/CT, although no signs of these systemic findings were described by clinical examination.

When comparing visual systemic manifestations between pSS patients with and without a lymphoma, only the presence of pulmonary nodules was significantly different between both patient groups (Table 2). For seven out of the eight lymphoma patients, these pulmonary nodules were clinically described as a MALT lymphoma location, of which four were confirmed to be pulmonary MALT lymphoma by biopsy. The remaining lymphoma patient with a pulmonary nodule was diagnosed with a primary lung carcinoma after FDG-PET/CT. The nodular lesions found in the three non-lymphoma patients were related to amyloidosis, lymphocytic interstitial pneumonia, and to a calcified hamartoma. pSS patients without lymphoma more frequently showed arthritis, PMR, multinodular struma and interstitial lung disease on FDG-PET/CT compared with lymphoma patients, but these findings were not significantly different. FDG uptake in cervical, axillary, mediastinal and inguinal lymph node regions was found frequently in pSS, and did not differ between pSS patients with or without a lymphoma (Table 2).

Quantitative analysis

The highest SUVmax and SUVpeak in the parotid and submandibular glands were significantly higher in pSS patients with lymphoma (at any location), compared with pSS patients without lymphoma (Table 2; Supplementary Table S1, available at *Rheumatology* online). Furthermore, lymphoma patients had increased frontal and transversal diameters of

Table 2. PET parameters of salivary and lacrimal glands and systemic regions in pSS patients with and without lymphoma

	Patients with pSS associated lymphoma ($N = 26$)	Patients without lymphoma ($N = 44$)	*P*-value
Parotid glands			
Visual uptake ≥2	22 (88.0)	20 (45.5)	**<0.001**
SUVmax	4.86 (3.01–8.71)	2.29 (1.69–2.86)	**<0.001**
Diameter (transversal), cm	3.31 (2.31–4.02)	2.62 (2.16–3.22)	**0.049**
Diameter (frontal), cm	4.49 (3.91–5.25)	3.32 (2.86–4.19)	**<0.001**
Submandibular glands			
Visual uptake ≥2	16 (66.7)	15 (34.9)	**0.012**
SUVmax	3.32 (2.60–6.52)	2.42 (1.66–2.83)	**<0.001**
Diameter (transversal), cm	1.60 (1.40–2.33)	1.70 (1.23–1.86)	0.471
Lacrimal glands			
Visual uptake ≥1	7 (28.0)	3 (6.8)	**0.029**
SUVmax	1.84 (1.43–2.63)	1.63 (1.37–2.00)	0.162
Lymphoid organs			
Lymph nodes			
Positivity in:			
Any region	21 (80.8)	31 (70.5)	0.340
Cervical region	13 (52.0)	16 (36.4)	0.206
Axillary region	13 (50.0)	19 (43.2)	0.580
Mediastinal region	10 (38.5)	21 (47.7)	0.451
Inguinal region	9 (34.6)	15 (34.9)	0.982
Bone marrow			
SUVmean	2.04 (1.86–2.51)	2.00 (1.53–2.43)	0.419
Spleen			
SUVmean	2.33 (2.04–2.57)	2.15 (1.80–2.45)	0.201
Diameter	9.51 (7.80–11.85)	8.72 (7.41–10.04)	0.315
Tonsils			
SUVmean	4.18 (3.35–5.04)	3.19 (2.79–4.49)	**0.022**
Other organs			
Visual positivity			
Arthritis	0 (0)	4 (9.1)	0.289
Myositis	1 (3.8)	1 (2.3)	1.000
Enthesitis	9 (34.6)	13 (29.5)	0.659
PMR	0 (0)	3 (6.8)	0.289
Vasculitis	0 (0)	0 (0)	NA
Nephritis	0 (0)	0 (0)	NA
Liver			
SUVmean	2.55 (2.17–2.76)	2.28 (1.81–2.47)	**0.024**
Diameter	17.1 (15.01–17.81)	16.88 (15.05–19.09)	0.644
Pancreas			
Visual pancreatitis	1 (3.8)	0 (0)	0.371
SUVmean	1.85 (1.56–2.08)	1.62 (1.29–1.93)	**0.021**
Thyroid gland			
Visual thyroiditis	0 (0)	1 (2.3)	1.000
Visual multinodular struma	1 (4.0)	5 (11.4)	0.406
SUVmean	1.60 (1.33–1.99)	1.54 (1.25–2.00)	0.837
Lungs			
Visual inflammatory	5 (19.2)	6 (13.6)	0.534
Visual interstitial	1 (3.8)	4 (9.1)	0.644
Visual lung nodule	8 (30.8)	3 (6.8)	**0.015**
SUVmean (normal lung parenchyma)	0.54 (0.47–0.67)	0.56 (0.41–0.68)	0.627

Data are presented as number (%) or median (interquartile range). Bold text highlights significant values. pSS; primary SS: SUVmax/SUVmean: maximum/mean standardized uptake value.

parotid glands. Correlations between SUVmax within the left and the right salivary glands were higher within the non-lymphoma group compared with the lymphoma group (parotid gland rho = 0.55 *vs* 0.77, submandibular gland rho = 0.81 *vs* 0.91). These findings indicate that glandular activity without lymphoma is usually bilateral, with comparable SUVs at both sides, whereas FDG uptake due to salivary gland lymphoma can be unilateral (Fig. 2). Although pSS patients with lymphoma more often showed visual FDG uptake ≥1 within the lacrimal glands, the SUVmax in the lacrimal glands was not significantly different between both patient groups (Table 2). SUVmean of tonsils, liver and pancreas were higher in patients with a lymphoma, but no differences were found in SUVmean of the bone marrow, spleen, thyroid glands and lung parenchyma between the two patient groups.

Combining visual and quantitative analysis to discriminate between lymphoma and non-lymphoma

The accuracy of the highest SUVmax of the parotid glands to predict lymphoma diagnosis (any lymphoma type, at any location) was good, with an AUC of 0.83 (95% CI 0.72–0.93)

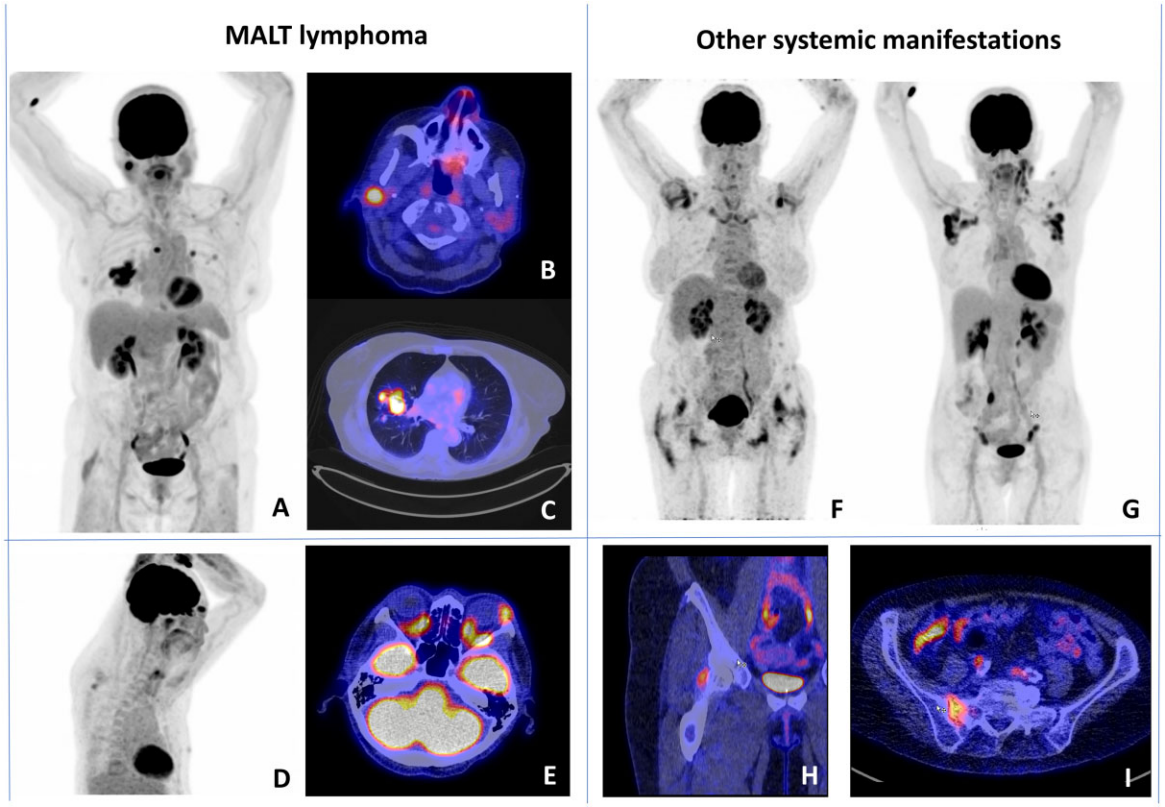

Figure 2. FDG-PET imaging of MALT lymphomas and other systemic manifestations in pSS. (**A–C**) pSS patient with parotid gland MALT lymphoma (biopsy side: right parotid gland) and pulmonary nodules on PET MIP image (**A**) and fused PET/CT images (**B**, **C**). (**D**, **E**) pSS patient with a lacrimal gland MALT lymphoma (left lacrimal gland). (**F–I**) Systemic manifestations of pSS found by FDG-PET/CT imaging. (**F**) PMR, with FDG uptake in shoulder and hip regions. (**G**) Intense FDG uptake in lymph node regions (head/neck, axillary and inguinal), histology axillary lymph node: no signs of lymphoma. (**H**) Enthesopathy hip region. (**I**) Arthritis right SI joint. FDG: [^{18}F]-fluorodeoxyglucose; pSS: primary SS; MALT: Mucosa Associated Lymphoid Tissue

and an optimal cut-off value of 3.1. For the highest SUVmax in the submandibular gland, the AUC was 0.79 (95% CI 0.62–0.91) with a cut-off value of 2.9 (Supplementary Table S2, available at *Rheumatology* online). Sensitivity and specificity of these cut-off values were 76% and 82% for the parotid gland and 67% and 84% for the submandibular gland, respectively (Table 3, Fig. 3). For the presence of nodular lung lesions, the only visual finding that was significantly different between lymphoma and non-lymphoma patients, specificity was high, but sensitivity was low. After combining these three visual and quantitative features (SUVmax parotid, SUVmax submandibular, nodular lung lesions), sensitivity increased to 92% in case at least one of these three features was present. When at least two out of these three features were present, specificity increased to 91%, but sensitivity decreased to 75% (Table 3). When performing the analysis in the subgroup of pSS patients who underwent FDG-PET/CT because of high clinical disease activity of pSS/suspicion of a pSS-associated lymphoma ($N = 65$), results were similar and sensitivities did not change (Supplementary Table S3, available at *Rheumatology* online).

Clinical correlations

Correlations between highest SUVmax of the salivary glands and ESSDAI total scores were fair (rho = 0.29 for both the parotid and submandibular gland). SUVmax in both salivary glands was, however, higher in patients with low and moderate activity in the glandular ESSDAI domain, compared with patients without glandular ESSDAI activity (Fig. 3). Poor to fair correlations were found between SUVmax of salivary glands and serological findings such as, IgG, RF and complement levels (data not shown). Patients with presence of pSS-specific histological features (lymphoepithelial lesions, plasma cell shift, germinal centres) in their parotid gland biopsies within 1 year from PET imaging showed no increased SUV in the biopsied parotid gland.

Discussion

In this cohort of patients with pSS, FDG-PET/CT was able to detect salivary gland and systemic abnormalities. pSS patients with a pSS-associated lymphoma showed higher FDG uptake in the parotid and submandibular glands, both visually and quantitatively, compared with non-lymphoma patients. Cut-off values of the highest SUVmax in the parotid (>3.1) and submandibular gland (>2.9) led to sensitivities of 67–76% and specificities of 82–84% to diagnose a pSS-associated lymphoma. As nodular lung lesions were mostly found in patients with a pSS-associated lymphoma, specificity was high (93%), but sensitivity was low. When these three quantitative and visual features were combined, sensitivity increased to 92% when at least one of the three features was present, with a negative predictive value of 94%. These findings indicate that FDG-PET/CT could assist in excluding a pSS-associated lymphoma when none of these three features is present, which possibly leads to a decrease of invasive biopsies in patients

Table 3. Sensitivity and specificity of PET parameters to discriminate between pSS patients with and without lymphoma

	Number of patients	Sensitivity	Specificity	PPV	NPV
Separate items					
Par SUVmax > 3.1	$N = 69$	76% (19/25)	82% (36/44)	70% (19/27)	86% (36/42)
Subm SUVmax > 2.9	$N = 67$	67% (16/24)	84% (36/43)	70% (16/23)	82% (36/44)
Presence of nodular lung lesions	$N = 70$	31% (8/26)	93% (41/44)	73% (8/11)	70% (41/59)
Combination scores					
1 out of 3 present	$N = 69$	92% (24/26)	67% (29/43)	63% (24/38)	94% (29/31)
2 out of 3 present	$N = 68$	75% (18/24)	91% (40/44)	82% (18/22)	87% (40/46)

pSS: primary SS; PPV: positive predictive value; NPV: negative predictive value; Par: parotid gland; Subm: submandibular gland; SUVmax: maximum standardized uptake value.

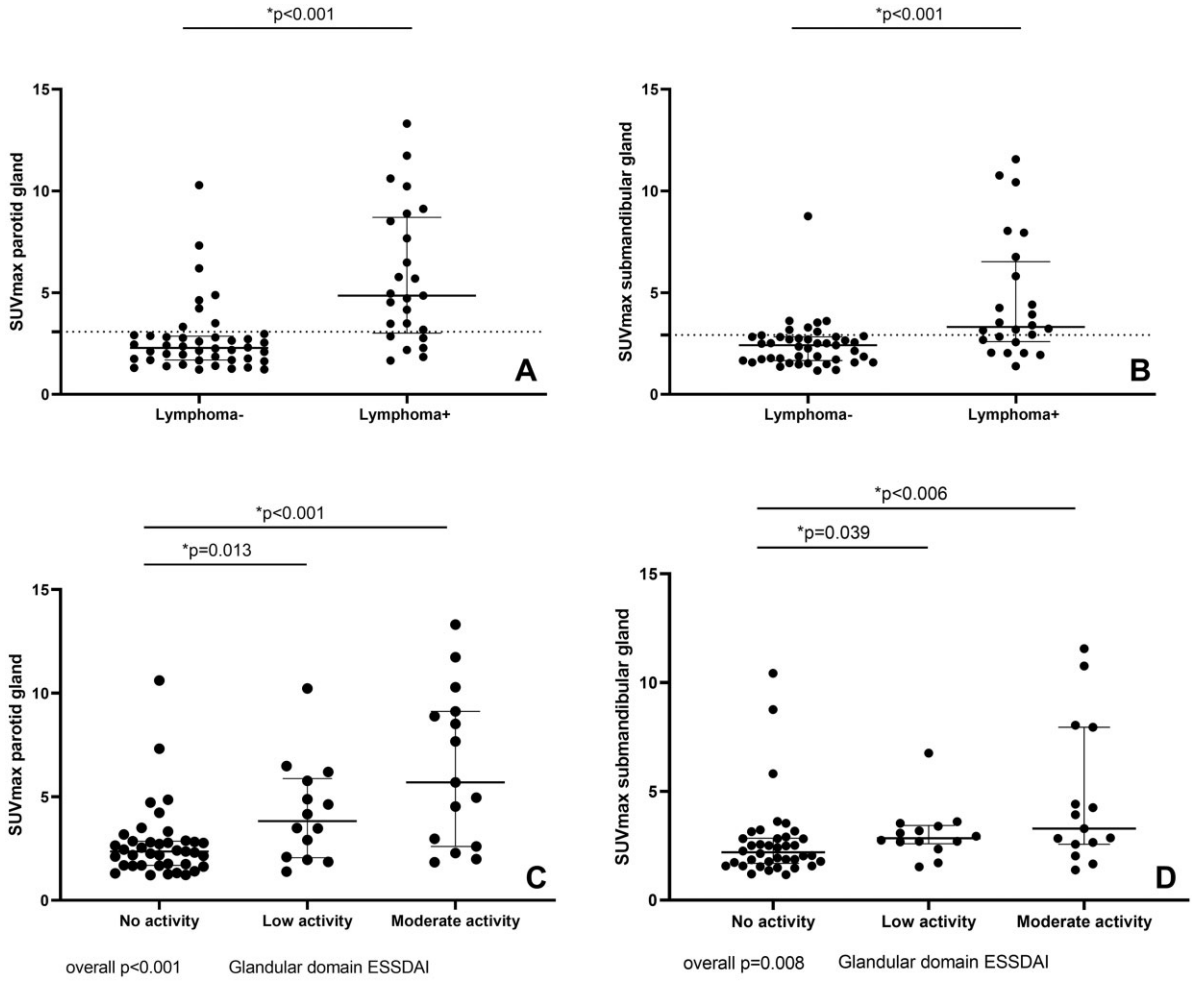

Figure 3. SUVmax within the parotid and submandibular glands in lymphoma and non-lymphoma patients and in patients with and without glandular activity in the ESSDAI. (**A, B**) PSS patients with a lymphoma have higher SUVmax compared to patients without a lymphoma, in both the parotid (**A**) and submandibular (**B**) gland. (**C, D**) SUVmax in the parotid (**C**) and submandibular (**D**) gland are higher in patients with low and moderate activity in the glandular ESSDAI domain, compared with patients without activity in the glandular ESSDAI domain. SUVmax: maximum standardized uptake values; pSS: primary SS; ESSDAI: EULAR SS DAI

without FDG-PET/CT abnormalities. Furthermore, FDG-PET/CT visualizes systemic manifestations in pSS, such as lung abnormalities, enthesitis and myositis. Interestingly, FDG uptake in lymph nodes was frequently found, but was not discriminative between patients with and without lymphoma.

When using the combination score of ≥ 1 out of 3 features for lymphoma diagnosis, two patients without PET features were missed in this cohort (sensitivity 92%, 24/26). However, both patients had clinical signs associated with parotid gland lymphoma (patient 1: cystic parotid gland swelling on palpation, cryoglobulinemia, low complement C4, presence of RF; patient 2: atypical globular lesion by parotid salivary gland US, presence of RF). In other words, clinical findings that are highly associated with the presence of a salivary gland lymphoma should always outweigh negative findings on

FDG-PET/CT. In these two patients, parotid SUVmax < 3.1 could be explained by the relatively small salivary gland abnormality (patient 1: <1cm, patient 2: 6 × 8 mm). Although the specificity of the combination of ≥2 features was high (91%), 4 out of 22 pSS patients with ≥2 features were clinically not described nor treated as lymphoma patients. In these patients, SUVs of the parotid and submandibular gland were higher than the cut-off values, but three of them did not undergo salivary gland biopsies after FDG-PET/CT, and salivary gland lymphomas could have been missed. Even though the results of this study indicate that biopsies are not always needed in patients without any PET features, biopsies are still of added value in patients with ≥1 or ≥2 PET features, to either confirm or rule out a lymphoma, or to discriminate between different lymphoma types or (transformation) to a high-grade lymphoma. FDG-PET/CT can assist in finding the best biopsy location, based on the combination of FDG avidity and biopsy accessibility. How FDG-PET/CT can guide to the best biopsy location is also shown in Fig. 2A, as the right parotid gland (and not the left) would be the best location based on FDG avidity. The potential presence of unilateral salivary gland MALT lymphomas was also shown by lower correlation coefficients between SUVmax within the right and left salivary glands in lymphoma patients, compared with non-lymphoma patients.

The results of this study confirm previous findings from a retrospective cohort of 45 pSS patients (15 with lymphoma, 30 without lymphoma), which also showed associations between parotid SUVmax, presence of nodular lung lesions and pSS-associated lymphomas [12]. However, SUVmax cut-off values differed, and Keraen *et al.* [12] did not find higher FDG uptake in submandibular glands of lymphoma patients. The differences between this study and our study could be explained by the fact that Keraen *et al.* used different camera systems without applying standardized guidelines and EARL reconstructions, and the SUVs of these non-standardized camera systems cannot directly be used by others. The differences in submandibular gland uptake could also be explained by differences in patient population. It is hypothesized that MALT lymphomas arise within salivary glands of pSS patients and they seem to be able to disseminate to other salivary glands or systemic sites [18, 19]. Therefore, it is possible that the number of patients with submandibular gland MALT involvement in our cohort is higher compared with the cohort of Keraen *et al.*, with subsequent higher SUVs. As submandibular gland biopsies were not performed in this cohort, we could not confirm submandibular gland MALT localization with clonal relationships in both parotid and submandibular gland biopsies. However, for one patient with MALT lymphoma in both the parotid gland and lungs, clonality analysis of *IGH* gene rearrangements showed a clear clonal relationship between the monoclonal B cells in both biopsies. Although two clonally identical lymphoma B cells could theoretically arise from a shared ancestor B cell at different glandular sites, the hypothesis that neoplastic B cells originate at one site (presumably the salivary gland) and subsequently disseminate to other sites seems more likely. A previous study on the mutational landscape of pSS-associated MALT lymphomas showed a low mutational burden and absence of driver mutations, which indicates that the chronic environment is required for neoplastic transformation, and may suggest that MALT lymphomas need to acquire more (driver) mutations before they disseminate [20].

FDG-PET can also be used to visualize systemic manifestations in pSS. FDG uptake was frequently seen in lymph nodes, entheses and lungs. FDG uptake in lymph nodes was also frequent in previous studies, without differences between lymphoma and non-lymphoma patients [12–14]. In this cohort, 31% of pSS patients showed FDG uptake in entheses, which is higher compared with healthy subjects (0.7%) [21]. The frequent presence of enthesitis might be an explanation for musculoskeletal pain not related to arthritis, which is a relatively common complaint among pSS patients. FDG-PET detected pulmonary abnormalities in 24 (34%) pSS patients, of which only 11 patients exhibited pulmonary symptoms such as cough or dyspnoea around the time of FDG-PET/CT, and 10 patients underwent high-resolution CT for pulmonary follow-up before FDG-PET imaging. This also illustrates that pulmonary abnormalities, i.e. MALT, and interstitial and inflammatory lesions, are frequent in pSS and can be subclinical/asymptomatic [22–24].

A limitation of this retrospective cohort is that it mostly consists of relatively active pSS patients who underwent PET imaging for staging or suspicion of a lymphoma. Frequencies of systemic manifestations in this cohort are therefore not representative for the total pSS population. Also, the cut-off values of SUVs found in this cohort should be validated in a validation cohort before they can be used as a diagnostic marker for lymphomas in pSS. However, the cut-off values found in this cohort can alert nuclear medicine physicians and rheumatologists of the potential presence of a lymphoma, and can assist in the decision whether a biopsy is needed or not. Although salivary gland MALT lymphomas are the most common lymphoma type in pSS, it would be interesting to confirm our results in patients with MALT lymphomas at different locations, e.g. gastric, as FDG avidity of MALT lymphomas located outside salivary glands and lungs seems to be lower [10, 11]. However, all patients with lymphomas located outside the salivary glands and lungs in our cohort (lacrimal glands and lymph nodes) did fulfil at least one of the three PET features, mostly the parotid and/or submandibular gland item.

In conclusion, FDG-PET/CT is able to visualize systemic manifestations in pSS, mostly affecting salivary glands, lymph nodes, lungs and entheses. FDG-PET/CT can assist in excluding pSS-associated lymphomas in patients without any PET abnormalities (this cohort: SUVmax parotid < 3.1, SUVmax submandibular < 2.9 and absence of nodular lung lesions), which could lead to a reduction of invasive biopsies in pSS patients suspected of having a lymphoma. When a biopsy is needed, FDG-PET/CT can guide to the best biopsy location.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

All data underlying this article are included in the article and in its online supplementary material. The data that support this study are available on a reasonable request to the corresponding author.

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