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Concise report

# Extra-articular findings with FDG-PET/CT in rheumatoid arthritis patients: more harm than benefit

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## Abstract

**Objective.** Whole-body PET with CT scanning using $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) is used occasionally in RA patients to detect arthritis. FDG-PET/CT might also detect malignancies, but the amount of incidental findings and the number of relevant malignant diseases that could be missed are currently unknown. We aimed to study the malignancy screening performance of whole-body FDG-PET/CT in longstanding RA patients with low disease activity.

**Methods.** FDG-PET/CT scanning was done in the intervention arm of the Dose REduction Strategy of Subcutaneous TNF-inhibitors (DRESS) study, a randomized controlled trial on dose-tapering of biological DMARDs. The reference standard was clinical diagnosis of malignancy during the 3-year follow-up period of the study. Prevalence of extra-articular abnormalities, follow-up and treatments were summarized post hoc.

**Results.** One hundred and twenty-one scans were carried out in 79 patients. Extra-articular abnormalities were found in 59 of 121 (49%) scans, resulting in additional diagnostic procedures in 21 of 79 (26.6%) patients. Nine patients (7.4%) were suspected of malignancy; none turned out to be malignant. Six clinical malignancies that developed during follow-up were all negative on baseline FDG-PET/CT.

**Conclusion.** Whole-body FDG-PET/CT scanning used in RA patients for imaging of arthritis results in frequent incidental extra-articular findings, whereas some who apparently had normal scans also developed malignancies.

**Trial registration.** Netherlands Trial Register, www.trialregister.nl, NL6771.

**Key words:** RA, TNF inhibitors, biological therapy

CLINICAL SCIENCE

**Key messages**

- Using $^{18}$F-fluorodeoxyglucose PET/CT for assessing arthritis in longstanding RA patients with low disease activity results in a substantial number of incidental findings.
- Some RA patients who apparently had normal scans also developed malignancies.
- Whole-body $^{18}$F-fluorodeoxyglucose PET/CT scanning with musculoskeletal indication requires patients to be properly informed of risks and benefits.

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## Introduction

Whole-body $^{18}$F-fluorodeoxyglucose (18F-FDG) PET scanning, often combined with low-dose CT scanning (FDG-PET/CT), has the ability to detect various malignancies non-invasively at potentially curable stages and is used as a diagnostic tool and for follow-up [1–3]. Other clinical indications for FDG-PET/CT include cardiac conditions (myocardial functioning), work-up of infectious and inflammatory diseases (fever of unknown origin) and neurological conditions (epilepsy and dementia) [4].

Although FDG-PET/CT is not recommended routinely for establishing and quantifying arthritis in the context of RA, it is occasionally used by physicians. Reasons to use FDG-PET/CT scans are to diagnose arthritis or guide decisions on systemic therapy, because FDG uptake in affected joints can reflect disease activity [5, 6]. Elzinga *et al.* [7] found that FDG-PET/CT of the hands and wrists might be used as a predictor of therapeutic response. Partly based on these findings, the EULAR recommendations for the use of imaging techniques for the joints in the clinical management of RA state: 'Inflammation seen on imaging may be more predictive of a therapeutic response than clinical features of disease activity; imaging may be used to predict response to treatment' [8]. However, no data are available on extra-articular incidental findings associated with the use of whole-body FDG-PET/CT scans for assessment of arthritis. Although whole-body FDG-PET/CT could be used as a cancer screening tool in asymptomatic adults, there are few data on this subject. This idea has been challenged conceptually for PET and other screening modalities [9–12]. Suboptimal test characteristics, especially low specificity, might increase the likelihood of false-positive or irrelevant abnormal findings, resulting in additional follow-up diagnostics/treatment and generating patient burden and costs. Likewise, suboptimal sensitivity of a test in the incorrect setting could lead to false reassurance in the case of a false-negative result. Procedural drawbacks of whole-body FDG-PET/CT scanning are exposure to radiation, patient burden, use of scarce resources and costs. Nevertheless, whole-body FDG-PET/CT is often perceived as a valuable whole-body screening tool by both patients and physicians.

In the DRESS trial [13–15], we performed baseline and follow-up whole-body FDG-PET/CT scans to assess arthritis activity in longstanding RA patients treated with TNF inhibitors (TNFi; a class of biological DMARDs), with close clinical monitoring of the patients during a 3-year period. This provided an opportunity to study the cancer screening performance of whole-body FDG-PET/CT in this specific population.

## Methods

Longstanding RA patients with stable disease activity treated with s.c. TNFi were randomized to either stepwise tapering or continuation of their TNFi [13–15]. Baseline whole-body FDG-PET/CT scans were performed in consenting patients in the tapering arm to assess the predictive value of subclinical PET-arthritis for risk of flaring [13]. Scanning was done with a Siemens Biograph mCT FDG-PET/CT scanner according to the European Association of Nuclear Medicine procedure guidelines, as described by Boellaard *et al.* [16]. The scanning protocol, arthritis scoring system and results on arthritis activity were reported elsewhere [17]. The scans were also read by experienced nuclear medicine specialists at the academic hospital immediately after they were performed for any unexpected extra-articular findings. At this time, a report was made of all incidental extra-articular findings, conforming to routine clinical care. The reader was not blinded for regarding the clinical information on the patient and reported results on a probability scale. When necessary, the treating phycician could consult the nuclear medicine specialist for further advice. One patient could show multiple abnormalities on one scan.

Patients were followed for 3 years, and all clinical outcomes and FDG-PET/CT-related follow-up diagnostics and treatments were noted. The reader who summarized the clinical outcomes retrospectively was not blinded for the FDG-PET/CT test result. Similar abnormalities found on both scans (in the case of repeated scans) were counted as one.

The DRESS study was performed at the Sint Maartenskliniek, from December 2011 to May 2014, and received ethical review board approval (number NL37704.091.11). This study was approved by the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, NL37704.091.11). Patients provided written informed consent.

## Results

Baseline FDG-PET/CT scans were performed in 79 patients, and in 42 patients a follow-up scan was performed at the time of maximal tapering/discontinuation (between 3 and 18 months after baseline, depending on whether and when a flare occurred). This led to a total number of 121 FDG-PET/CT scans.

### Incidental findings

One or more abnormal results were found in 45 of 79 (57%) patients and on 59 of 121 (48.8%) scans. Extra-articular abnormal results are specified in Table 1. Of these 59 abnormal scan results, the research physician (consulting with a nuclear medicine specialist) categorized 36 (61%) scan results as clinically insignificant, and no further action was undertaken.

Follow-up action was undertaken for 23 (39%) abnormalities in 21 patients, which could consist of referral to a specialist or reassessing and/or scheduling diagnostics directly by the treating rheumatologist (Table 2). In five (6.3%) patients, the rheumatologist followed-up.

**Table 1** Abnormalities found on $^{18}$F-fluorodeoxyglucose PET/CT scans

| Parameter | Abnormal results found on scans, *n* (%) |
|---|---|
| No PET/CT result obtained | 3 (2.5) |
| Claustrophobia | 2 |
| Moved during scan | 1 |
| No abnormalities found on any scan | 59 (48.8) |
| One or more abnormalities found per scan[a] | 59 (48.8) |
| Total | 121 |
| Inflammatory | 7 (5.7) |
| Upper respiratory tract infection | 3 |
| Mediastinal lymphadenopathy | 3 |
| Pneumonia (known) | 1 |
| Suspected malignancy | 9 (7.4) |
| Breast, caecum, uterus, lymphoma, adrenal, larynx, sigmoid, pulmonary, prostate | 9 |
| Cardiovascular | 2 (1.6) |
| Aneurism | 2 |
| Pulmonary | 7 (5.8) |
| Nodules | 6 |
| Pleural thickening | 1 |
| Gastrointestinal | 10 (8.3) |
| Gallstones | 1 |
| Oesophagitis/gastritis | 5 |
| Intestinal/rectal focal lesions (non-specific) | 4 |
| Muscles/tendons | 3 (2.5) |
| Bone-related | 3 (2.5) |
| Fractures (known) | 1 |
| OA/osteoporosis[b] | 2 |
| Hypermetabolic lymph nodes (non-specific) | 16 (13.2) |
| Thyroid | 4 (3.3) |
| Enlarged | 1 |
| High uptake/metabolism (diffused) | 3 |

[a]Fifteen of these abnormalities were found on the second PET/CT; the rest was found on the first scan. Eleven abnormalities on the second PET/CT were the same as the one seen on the first scan, and seven abnormalities resolved after the first scan. One scan can show multiple abnormalities, from different categories. [b]Suggestive image on CT.

In three cases (Table 2: patients 6, 12 and 14), this follow-up took place without referral to another specialist. In the first patient, physical examination of the thorax and lungs took place, and an X-ray was conducted. In the second patient, a skin lesion was examined. In a third patient, the thyroid was examined clinically and thyroid-stimulating hormone (TSH) was assessed. These tests did not result in clinically relevant abnormal findings. In two cases (Table 2: patients 5 and 21) the rheumatologist referred the patient to another specialist. In the first patient, clinical evaluation of the tonsils took place, after which the patient was referred to an ENT specialist. In the second patient, the thyroid was examined clinically, after which the patient was referred to an endocrinologist. The ENT specialist examined the thyroid clinically after 6 and 12 months to follow-up but did not find any clinically relevant abnormalities.

For 19 (32.2%) abnormalities in 17 (21.5%) patients, a consultation with a different specialist was scheduled. One patient (Table 2: patient 20) consulted two specialists (an ENT specialist and a urologist), but no additional diagnostics or treatments were performed.

### Non-invasive treatment

In one patient (Table 2: patient 17) an US examination, which was conducted after the abnormalities found on the FDG-PET/CT, found an aneurysm of 43 mm immediately above the aortic bifurcation. Referral to a vascular surgeon resulted in advice regarding lifestyle interventions and statins. In another patient (Table 2: patient 5), who was referred by the rheumatologist, the throat was diffusely tender on palpation. Given that a tonsillectomy previously took place and owing to globus sensation in the throat combined with a productive cough, the ENT specialist prescribed antibiotics. Thereafter, the follow-up was expectant, and no standard follow-up consultation was planned.

### Surgical interventions

One patient (Table 2: patient 13) with an enlarged thyroid gland was referred to internal medicine, after which US examination showed a non-homogeneous hypervascular nodule that took up most of the enlarged left thyroid gland, with focal calcifications and cystic components. Thyroid fine needle aspiration biopsy was performed three times, and all were inconclusive. A hemi-thyroidectomy was performed, and the mass turned out to be a follicular adenoma. This resection was complicated by persistent recurrent laryngeal nerve paresis and hoarseness.

In another patient (Table 2: patient 15), irregularities were found on the cervical smear test. A subsequent US examination showed a myoma located in the uterus. This was followed by a myomectomy. In a third patient (Table 2: patient 9), a colonoscopy was performed based on the FDG-PET/CT scan results, and two polyps were found in the rectosigmoid colon, both of which were resected. Histopathology of the two colonic polyps showed two low-grade adenomas. A follow-up colonoscopy was planned 5 years after the polyp resection.

In a fourth patient (Table 2: patient 18), an emergency consultation with an ENT specialist was planned based on the FDG-PET/CT scan, which showed a hypermetabolic process in the larynx without clinical symptoms, initially suspected to be activity of the vocal cords. After review, however, the abnormality was diagnosed as a thyroglossal cyst. Eventually, a sistrunk procedure was performed to extract the cyst in the neck.

Lastly, a patient (Table 2: patient 10) with the FDG-PET/CT scan showing a paraspinal muscle mass (level L3/L4) underwent marginal myotomy after multidisciplinary consultation. The abnormality turned out to be a benign schwannoma.

**Table 2** Follow-up diagnostics and treatment after abnormal $^{18}$F-fluorodeoxyglucose PET/CT scan

| Patient | Consultation with rheumatologist | Consultation with other specialist | Follow-up diagnostics | Non-invasive and surgical intervention | Conclusion and diagnosis |
|---|---|---|---|---|---|
| 1 | – | Pulmonologist | – | – | Increased FDG uptake in the right inferior lobe of the lungs combined with several nodules. However, no malignancy/other clinically relevant diagnosis. No further action |
| 2 | – | Internal medicine<br>Internal medicine[a] | CT of thorax<br>CT of colon + colonoscopy | – | Increased FDG uptake in hilar/mediastinal lymph nodes and intestines. No malignancy/other clinically relevant diagnosis. No further action |
| 3 | – | General practitioner | Mammogram + US of breast | – | Increased FDG uptake in breast tissue. No malignancy/other clinically relevant diagnosis. No further action |
| 4 | – | Dermatologist | – | – | Increased FDG uptake in tissue on the right upper leg. No malignancy/other clinically relevant diagnosis. No further action |
| 5 | Clinical evaluation of tonsils at next planned consultation | ENT specialist | – | Antibiotics | Increased FDG uptake owing to previously performed tonsillectomy. No further action |
| 6 | Physical examination of thorax and lungs | – | X-ray of thorax | – | Increased FDG uptake dorsally around the 10th rib. No malignancy/other clinically relevant diagnosis. No further action |
| 7 | – | ENT specialist | – | – | Increased FDG uptake owing to speaking during scan. No further action |
| 8 | – | Internal medicine[b] | – | – | Increased FDG uptake in hilar/mediastinal lymph nodes and intestines. No malignancy/other clinically relevant diagnosis. No further action |
| 9 | – | Internal medicine | Colonoscopy with polyp resection | – | Two low-grade adenomas. A follow-up colonoscopy was planned after 5 years post-resection |
| 10 | – | Internal medicine | – | Marginal myotomy paraspinal muscle mass | Schwannoma |
| 11 | – | Pulmonologist | – | – | Increased nodular FDG uptake in the basal segment of the left lung. Turned out to be a stable rheumatoid nodule |
| 12 | Clinical evaluation of skin lesion at next planned consultation | – | – | – | Increased FDG uptake at cutaneous lesion in axilla/upper arm. No malignancy/other clinically relevant diagnosis. No further action |
| 13 | – | Internal medicine | Fine needle aspiration biopsy (3×) + laboratory testing | Hemithyroidectomy | Benign follicular adenoma |

(continued)

TABLE 2 Continued

| Patient | Consultation with rheumatologist | Consultation with other specialist | Follow-up diagnostics | Non-invasive and surgical intervention | Conclusion and diagnosis |
|---|---|---|---|---|---|
| 14 | Evaluation of TSH and palpation of thyroid at next planned consultation | – | – | – | Increased FDG uptake in the thyroid. No malignancy/ other clinically relevant diagnosis. No further action |
| 15 | – | Gynaecologist | Cervical smear test + US of uterus | Myomectomy | Myoma in the uterus |
| 16 | – | – | CT thorax + abdomen | – | Increased FDG uptake in the lungs and adrenal glands. No malignancy/other clinically relevant diagnosis. No further action |
| 17 | – | Vascular surgeon | US of abdominal aorta | Statins and advice for lifestyle interventions | Aneurysm of the abdominal aorta (43 mm) + atherosclerosis |
| 18 | – | ENT specialist[b] | – | Cyst extraction in the right medial side of the neck via sistrunk procedure | Thyroglossal cyst |
| 19 | – | Pulmonologist | CT of thorax (2×, after 6 and 18 months) | – | Increased nodular FDG uptake in the inferior lobe of the right lung. Turned out to be a stable nodular lesion |
| 20 | – | ENT specialist Urologist | – | – | Increased FDG uptake in larynx and prostate. No malignancy/other clinically relevant diagnosis. No further action |
| 21 | Clinical evaluation of thyroid at next planned consultation | Endocrinologist | Clinical evaluation of thyroid after 6 and 12 months | – | Increased FDG uptake in thyroid. No malignancy/other clinically relevant diagnosis. No further action |

[a]Telephone consultation. [b]Emergency consultation. FDG, fluorodeoxyglucose; TSH, thyroid-stimulating hormone.

### Development of malignancy

None of the 9 of 79 (7.4%) suspected malignant lesions on PET/CT scan were confirmed to be or developed into a malignancy. During the 3-year follow-up, six clinical malignancies (bladder, penile, lymphoma, 2× melanoma and prostate) were found in six patients. None of these malignancies had been identified by the study-related whole-body FDG-PET/CT scans (Supplementary Table S1, available at *Rheumatology Advances in Practice* online). The malignancies were diagnosed after an interval of between 5 and 34 months, with a mean of 13 months (Supplementary Table S2, available at *Rheumatology Advances in Practice* online).

## Discussion

This study is the first to highlight the incidental extra-articular findings and test characteristics of whole-body FDG-PET/CT scans for malignancy in a population of longstanding RA patients with low disease activity treated with biologic DMARDs. A large number of extra-articular abnormalities was found, leading to follow-up consultations, additional (invasive) diagnostic testing, referral to other specialists and, in some cases, treatment. These were associated with anxiety, patient burden, costs and adverse effects. Conversely, the diagnostic value for malignancies was low.

Our study has some limitations concerning the conclusion regarding test characteristics for malignancy. It should be taken into consideration that test characteristics of whole-body FDG-PET/CT scans depend on the type and stage of a malignancy. For example, bladder and penile carcinoma are not visualized very well on FDG-PET/CT owing to urine contamination. For prostate carcinoma, there is no indication for FDG-PET/CT, because prostate-specific membrane antigen PET scan is better suited for this type of tumour. In the case of lymphomas, imaging on whole-body FDG-PET/CT scans is strongly dependent on the tumour subtype.

The major difference of this study compared with a standard diagnostic test accuracy study is the lack of blinding for the FDG-PET/CT assessment, with subsequent diagnostic analyses in patients. This could, however, only have led to overestimation of test accuracy, not to underestimation.

This study paints a sobering picture of the risks and benefits of whole-body FDG-PET/CT scanning in long-standing RA patients with low disease activity treated with biologic DMARDs. Using FDG-PET/CT scanning for assessing arthritis results in a substantial number of incidental findings, whereas some who had apparently normal scans also developed malignancies. Based on our findings, the use of whole-body FDG-PET/CT scanning for a musculoskeletal indication, either in case of research or as a clinical tool, requires properly informing patients of risk and benefits of this type of imaging.

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## Data availability statement

Additional unpublished data can be obtained from the corresponding author upon reasonable request.

## Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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