Systematic Review

The role of positron-emission tomography in the diagnosis of giant cell arteritis

A systematic review and meta-analysis

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Abstract

Background: **Giant cell arteritis (GCA) is an inflammatory disease of the larger vessels, typically affecting the temporal arteries, but involvement of the carotid and thoracic arteries is not uncommon. Serious complications such as blindness can occur if the disease is left untreated. Currently, the gold standard test for GCA is a temporal biopsy, but this invasive technique is not without risks and frequently inaccurate. We investigate the use of 18-fluoro-desoxyglucose (18F-FDG) positron emission tomography (PET) as a new diagnostic means in GCA.**

Methods**: We performed a literature search in the MEDLINE database for original research articles written in the English language that discussed the use of PET in diagnosing GCA. After applying selection criteria, 9 articles were included for literature review and 4 of these were incorporated in a meta-analysis.**

Results**: 18-FDG uptake in the extracranial arteries is correlated to the presence GCA within patients suspected for vasculitis. In our meta-analysis we found the following results: sensitivity 85% (95% CI; 74-92%, I2=0.0%), specificity 91% (95% CI; 82-96%, I2=31.2%), positive likelihood ratio 7.18 (95% CI; 3.43-15.06, I2 =10.1%) and negative likelihood ratio 0.19 (95% CI; 0.11-0.33, I2= 0.0%).**

Discussion**: 18F-FDG-PET cannot replace temporal artery biopsy at the present time, because of its limited ability to visualise the cranial arteries. However, PET may be provide valuable information when extracranial involvement is suspected, specifically in biopsy-negative patients who are strongly suspected of having GCA.**

Background

Giant cell arteritis (GCA) is one of the two types of large vessel vasculitis, as classified according to the 2012 Revised International Chapel Hill Consensus Conference.[1] GCA is the most common primary systemic vasculitis in adults and usually occurs in those over the age of 50 years. This age criterion distinguishes GCA from the other type of large vessel vasculitis, Takayasu's arteritis, a disease phenotypically similar to GCA but most commonly occuring in those aged younger than 50 years.[1]

Histopathologically, however, Takayasu's arteritis and GCA are indistinguishable.[1] GCA typically affects the temporal arteries, but involvement of the aorta and its major branches, mainly the branches of the carotid and vertebral arteries, is often observed. With the increasing use of novel imaging techniques, large vessel involvement is more frequently recognized.[2,3]

GCA is the most common primary systemic vasculitis in adults. In Europe and North America, the estimated prevalence is 200 per 100 000 and the incidence is 20–30 per 100 000.[4-8] If left undiagnosed, the disease progresses and can result in audiovestibular dysfunction, generalised peripheral polyneuropathy, stroke, myocardial infarctions, and blindness.[9-12]

The clinical presentation varies significantly between cases and diagnosing CGA can be difficult, but a variety of diagnostic tools are helpful in the diagnosis of GCA. These include haemoglobin counts, ESR/CRP, liver biochemistry and, most importantly, temporal artery biopsies. Because the latter test produces far more specific results than the former three [13], a positive temporal artery biopsy is currently regarded as the gold standard in the diagnosis of GCA.[14]

However, this gold standard test is not without its limitations. In their 1983 study, Hall and colleagues [15] already found that its sensitivity is not ideal (85%). They also remarked that in other, similar studies, sensitivity had varied between 67% and 97%. In these studies, a diagnosis of GCA was made using other strong radiological, pathological or clinical evidence.[15,16] This means that the current gold standard test will still leave more than 1 in every 10 patients undiagnosed. These results appear to hold true in more recent research, as a Spanish study [17] conducted in 2001 found that 29 of 190 patients with proven GCA had a negative initial temporal artery biopsy.

Biopsies might be negative because the biopsy missed the pathologically inflamed area, or because the GCA has an atypical phenotype and does not involve the temporal arteries.[18] Such extracranial involvement can occur in up to 74% of GCA patients.[19]

The current imperfect gold standard and the serious morbidity and mortality that are associated with GCA led us to investigate alternative methods of diagnosing the disease. One such method is the use of positron emission tomography with or without computed tomography (PET or PET-CT) to detect large vessel inflammation or extracranial involvement secondary to GCA. PET has shown promise in detecting extracranial involvement of GCA in previous research.[19-22] A PET scan is a non-invasive assessment technique compared to temporal artery biopsies. Hemorrhage and facial nerve injury have been reported as complications of the biopsy procedure.[23,24] In addition, several studies report that PET has proven useful in diagnosing patients with fever or inflammation of unknown origin [25-27] and patients with large vessel vasculitis.[28-30] Therefore, the objective of this review is to determine whether PET, with or without an added CT component, is a valuable addition to the current diagnostic work-up of GCA.

Methods

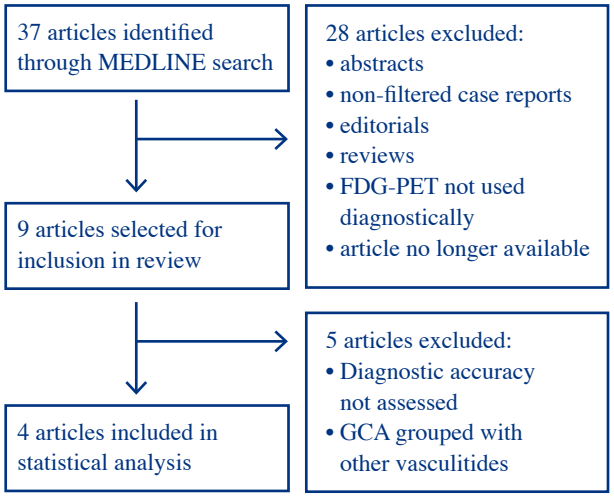
Literature search

We performed a search in the MEDLINE database for articles written in the English language that addressed the use of 18-FDG PET in the diagnostic process of GCA, up to September 2014. The exact MeSH-query we used was the following:

("Giant Cell Arteritis/diagnosis"[Majr] OR "Giant Cell Arteritis/radiography"[Majr] OR "Giant Cell Arteritis/radionuclide imaging"[Majr]) AND (("Radionuclide Imaging"[majr]) OR ("Positron-Emission Tomography"[Mesh])OR ("Fluorodeoxyglucose F18/diagnostic use"[Mesh])) AND ("humans"[MeSH Terms] AND English[lang]) NOT "Case Reports"[ptyp]

We excluded case reports in our search query, because these do not provide systematically conducted clinical research for analysis. Three authors screened the abstracts independently for eligibility. During this process, a further selection was made based on the exclusion of abstract-only articles, non-filtered case reports, editorials, comment- and response articles, reviews, and papers that did not discuss the use of 18-FDG-PET in the diagnostic process of GCA. Consensus was reached in case of disagreement between authors during the screening process. Full-text versions of the remaining articles were read and their references screened for other suitable articles. Papers thus found were included in our literature review. Additionally, those articles which provided Bayesian numerical data (e.g. numbers of true positives, true negatives, false positives and false negatives) relevant for assessment of the diagnostic accuracy of PET for GCA were included in a meta-analysis. Papers providing such data in incomplete form were included only if backwards calculation of sensitivity and specificity were possible. Our last search was performed on October 3, 2014. The selection process is shown in figure 1.

Figure 1- Data selection procedure of literature review and statistical analysis



Statistical analysis

Where applicable, we recorded the number of true positives, true negatives, false positives and false negatives provided by the respective authors, as found by PET-scanning using clinical criteria or positive temporal artery biopsies as the gold standard. In case the authors provided only part of this data, we reversely calculated the remainder of the data manually using Bayesian mathematics. This data was subsequently pooled and an overall sensitivity and specificity were determined. Additionally, an overall negative likelihood ratio (NLR) and positive likelihood ratio (PLR) were calculated with a random effects model. Between-study heterogeneity was assessed by means of an I2-test. Calculations were carried out by MetaDiSc version 4.1.[31]

Results

Literature review

The primary literature search yielded 37 articles, 9 of which were selected for inclusion in our literature review after excluding non-suitable articles (figure 1).

Walter et al. [32] used a four-category visual grading to evaluate 18F-FDG-uptake in a total of 30 PET-scans in patients with clinically confirmed GCA or Takayasu's arteritis. ESR ($p=0.007$) and CRP levels ($p=0.005$) in patients were found to be significantly positively correlated with the score these patients were assigned on a visual grading scale used for quantifying active inflammation, applied after PET-scanning. High ESR/CRP levels were also associated with a higher sensitivity of the PET-scan for the presence of large-vessel vasculitis compared to non-elevated ESR/CRP values (up to a maximum of 96% sensitivity at a CRP level of 130). Data analysis showed an overall sensitivity of 60% and a specificity of 99.8%. Walter and colleagues conclude that high ESR or CRP levels increase the sensitivity of PET as a diagnostic tool.

Blockmans et al. [33] conducted a study to evaluate the use of 18F-FDG-PET in GCA and polymyalgia rheumatica (PMR). In a cohort of 25 patients with clinical symptoms associated with GCA or PMR, a PET-scan of the thoracic, femoral and tibial arteries was performed and assessed using a four-category scoring system similar to the system used by Walter et al..[32] Vascular uptake in thoracic arteries was significantly more frequently observed ($p<0.0001$) in patients with GCA. Uptake in the thoracic arteries was associated with a sensitivity of 56% and a specificity of 98% for the diagnosis of GCA or PMR. Vascular uptake in the legs displayed a sensitivity of 64%, but a specificity of 77%. The authors speculate that this might be explained by the fact that arteriosclerosis is more frequently observed in the lower legs.

These authors subsequently set up another study [34] to assess 18F-FDG uptake in different parts of the vascular system and the larger joints at diagnosis and after three and six months of corticosteroid therapy. 35 patients with proven GCA underwent a PET-scan, which was scored at seven different vascular regions using the same scoring system as applied in their previous research. This resulted in a so-called total vascular score (TVS) ranging from 0 (no regions involved) to 21 (all regions involved). At baseline 29 out of 35 patients showed vascular uptake, most frequently (74%) in the subclavian arteries. In contrast with the aforementioned research by Walter et al. [32], patients with vascular 18F-FDG uptake had a significantly lower ESR ($p=0.039$) compared to those without vascular uptake in this study. After three months of corticosteroid therapy, mean TVS dropped to 2.4 ± 3.5 compared to baseline ($p<0.0005$) in 14 out of 22 patients who underwent a second PET-scan. After six months there was no further significant decrease in mean TVS in the 8 patients who still showed 18F-FDG uptake at this point. TVS did not differ significantly between patients who did and did not relapse.

In line with the results of the study conducted by Walter et al. [32], Hooisma et al. [35] found that an elevated ESR was a statistically significant positive predictor for a positive 18F-FDG-PET-scan in cases of confirmed large vessel vasculitis. Additionally, the presence of arthralgia was determined to be a statistically significant negative predictor of a positive 18F-FDG-PET-scan. However, because these predictive effects were very weak, Hooisma et al. concluded that these parameters would be of little clinical relevance.

18F-FDG-PET was not found to be a sensitive diagnostic tool by Brodmann et al. [36], who hypothesized that like duplex ultrasonography, 18F-FDG-PET would be able to detect inflammation of small vessels such as the temporal arteries. However, 18F-FDG-PET was unable to detect inflammation in 17 patients with GCA which only involved the temporal arteries, as confirmed by ultrasound. It should be noted that in accordance with the results found using ultrasound, PET did detect inflammation of the large vessels in all of the remaining 5 patients, who only had extracranial manifestations of GCA.

Hautzel et al. [21] investigated the degree of 18F-FDG uptake in the thoracic aorta compared to uptake in the liver, which invariably shows homogenous uptake, as a reference organ. They quantified the maximal standardised uptake value (SUVmax) in predetermined regions of interest (ROI) in both of these organs. Subsequently, a cut-off ratio between these organs associated with an optimal sensitivity and specificity of the PET-scan was determined using a receiver operating characteristic (ROC). The study involved a cohort of 18 GCA patients and two control groups. The participants in the first control group were age- and sex-matched patients who underwent a PET-scan for oncological reasons but had no history of malignant mediastinal, pulmonary or liver processes; the second control group contained age- and sex matched participants with at least one elevated liver enzyme value. Other inclusion criteria in this group were identical to those for the other control group. An optimal cut-off value was identified in a comparison between the GCA group and the first control group, corresponding with a sensitivity of 88.9% and a specificity of 95.1%. Applying this cut-off ratio to the control group with elevated liver enzymes revealed a specificity of 95.6%. The authors did not provide a sensitivity in this study.

Like Hautzel et al. [21], Prieto-Gonzalez et al. [19] determined sensitivity and specificity cut-off values for vascular inflammation as seen on PET/CT. A total of 32 patients were included, of whom 17 had used corticosteroids for a maximum of three days prior to scanning. The control group was comprised of 20 patients undergoing PET-scans for oncologic reasons. ROIs for 18F-FDG uptake were four aortic segments and their loco-regional tributaries, all normalised to liver 18F-FDG uptake, and SUVmax was determined quantitatively at each of these ROIs. SUVmax at every ROI was significantly higher in GCA patients compared to controls. The optimal cut-off value (1.89) provided a sensitivity of 80% and a specificity of 79%. Patients with cranial symptoms presented significantly higher values of maximal and mean SUVmax than patients lacking cranial manifestations. In agreement with the studies by Hooisma et al. [35] and Walter et al. [32], mean SUVmax correlated with CRP levels.

Besson et al. [20] attempted to identify a new semi-quantitative standard for assessing the presence of aortic wall inflammation in GCA on 18F-FDG-PET-scans. The study included 11 patients with biopsy-proven GCA, 8 of whom were undergoing corticosteroid therapy, and 11 controls. ROIs investigated included the ascending aorta, aortic arch and descending thoracic aorta. In these regions the SUVmax of 18F-FDG was determined semi-quantitatively and normalised to either lung, liver or venous blood pool uptake. The aortic to blood pool uptake ratio was found to be the most discriminative between the two cohorts. When applied to the aortic arch this method provided the best diagnostic performance, providing a sensitivity and specificity of 82% and 91%, respectively. CRP levels were found to correlate with the amount of uptake of the ascending aorta in the GCA group, in consonance with research by Walter, Hooisma and Hautzel and their respective colleagues.[21,32,35]

In a cohort including a total of 13 patients with GCA (n=10) or Takayasu's arteritis (n=3), stratified by age, Henes et al. [22] found increased SUVmax of 18F-FDG in the ascending and descending aorta and supra-aortic branches in 9 out of 10 GCA patients. The one patient who did not have increased SUVmax was receiving steroid therapy when the PET-scan was performed.

Table 1 - Characteristics of studies included in meta-analysis.

Study	Year	Design	PET-scoring system	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ration (95% CI)	Nagative Likelihood Ration (95% CI)
Prieto-Gonzalez et al.	2014	Prospective, case-control	Mean of four SUVmax-values in four different aortic segments	26	4	16	6	0.81 (0.64-0.93)	0.80 (0.56-0.94)	4.06 (1.66 - 9.91)	0.23 (0.11 - 0.50)
Besson et al.	2014	Retrospective, case-control	SUVmax-ratio artery/liver, artery/lung and artery/venous blood pool	9	1	10	2	0.82 (0.48-0.98)	0.91 (0.59-1.00)	9.00 (1.36-59.54)	0.20 (0.06-0.71)
Henes et al.	2008	Retrospective	Maximum of six SUVmax-values measured in six arterial locations	9	0	8	1	0.90 (0.55-1.00)	1.00 (0.63-1.00)	15.55 (1.04-232.22)	0.14 (0.03-0.64)
Hautzel et al.	2008	Retrospective, case-control	SUVmax-ratio aorta/liver	16	2	34	2	0.89 (0.65-0.99)	0.94 (0.81-0.99)	16.00 (4.12 - 62.14)	0.12 (0.03-0.44)

TP = true positives, FP = false positives, TN = true negatives, FN = false negatives, CI = confidence interval, LR = likelihood ratio, SUVmax = maximum standardised uptake value

However, 5 other patients in this group were also on steroid therapy during the PET-procedure. No patients in the control group, composed of 8 oncologic patients, showed pathological 18F-FDG uptake. By means of our own calculations, we determined the sensitivity and specificity to be 90% and 100%, respectively.

Meta-analysis

Of the 9 articles selected for literature review, 4 were included in the statistical analysis. The remaining articles were excluded from analysis because they did not assess the diagnostic accuracy of PET in GCA in terms of specificity and sensitivity (Blockmans et al. (2006), Hooisma et al.), only compared the efficacy of PET with the efficacy of another diagnostic technique (Brodmann et al.), or analysed a heterogeneous cohort of patients with different types of vasculitis as opposed to GCA only, thus confounding the statistical data. (Blockmans et al. (2000), Walter et al.). The characteristics of the studies included in the meta-analysis are presented in table 1. The outcome of the meta-analysis is presented in figures 2 through 5. Overall sensitivity was determined to be 85% (95% CI; 74-92%, I2=0.0%), overall specificity was determined to be 91% (95% CI; 82-96%, I2=31.2%), positive likelihood ratio was determined to be 7.18 (95% CI; 3.43-15.06, I2 =10.1%) and negative likelihood ratio was determined to be 0.19 (95% CI; 0.11-0.33, I2= 0.0%).

Discussion

At 85% sensitivity and 91% specificity, our own analysis confirms that PET is an accurate diagnostic tool for GCA. Although the resolution of PET has improved in recent years, visualisation of the temporal arteries remains very difficult because of the high uptake of 18F-FDG in the brain and the small size of the cranial vessels.[36,37] This limitation was also found by Brodmann et al. [36], who found that PET was unable to detect temporal inflammation but flawlessly identified extracranial involvement.

Figure 2 - Sensitivity Forest Plot. CI = confidence interval

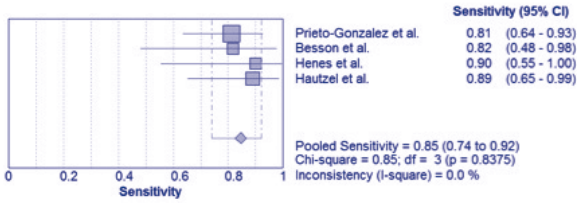


Figure 3 - Specificity Forest Plot. CI = confidence interval

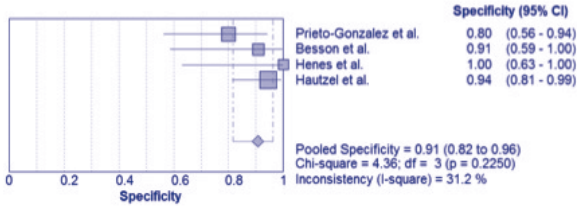


Figure 4 - Positive Likelihood Ratio (LR) Forest Plot. CI = confidence interval

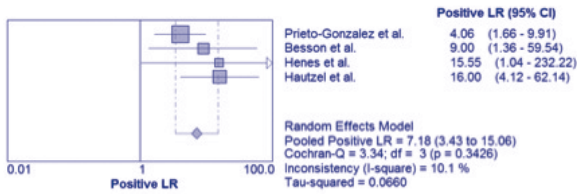
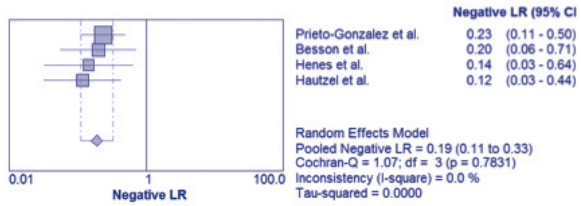


Figure 5 - Negative Likelihood Ratio (LR) Forest Plot. CI = confidence interval



The sensitivity of the biopsy procedure has been reported to vary between 67% and 97% (the most common value appearing to be around 80-85%)[15-17] but its specificity is often not reported. The sensitivity we found in our meta-analysis for PET appears almost identical. Because of the aforementioned difficulties in visualising the temporal arteries with PET, we do not recommend replacing temporal artery biopsies with PET as the first diagnostic modality of choice. However, PET might be very well suited to demonstrate GCA in patients with a negative biopsy but suspected extracranial involvement. PET could potentially reach even higher sensitivity and specificity in these cases because its limited ability to visualise the cranial vessels would be taken out of the equation.

Several issues arise in the interpretation of our meta-analysis and the literature we base our recommendation on. First of all, no standard protocol for the scoring of PET scans currently exists. Several authors have attempted to design a novel scoring system in their research. Hautzel et al. [21] proposed the use of a semi-quantitative scoring system based on the ratio between the SUVmax measured in the aorta and the liver. However, in a head-to-head comparison between different semi-quantitative scoring systems by Besson et al. [20], the aorta to liver ratio was outperformed by the aortic to venous blood pool SUVmax ratio. The latter study was methodically superior (but used a significantly smaller cohort) because all patients had biopsy-proven GCA, versus only clinical suspicion in the study by Hautzel et al. [21], and a carefully selected control group. For further research into the diagnostic performance of PET in GCA, we suggest the adoption of a semi-quantitative scoring system as opposed to a quantitative scoring system, because a semi-quantitative system generally achieves lower intra- and inter-observer variability.[38] We recommend the use of the aortic to venous blood pool SUVmax ratio using a cut-off value of 1.53, as proposed by Besson et al. [20], in order to achieve an optimal sensitivity and specificity.

Several studies included in our review reported difficulties in distinguishing atherosclerosis from vasculitis on PET imaging. Atherosclerosis can produce an image similar to vasculitis, because increased macrophage metabolism in this disease process increases 18F-FDG uptake in the vessel walls. CT provides a solution in dealing with this difficulty, even without the use of intravenous contrast (which could introduce attenuation errors). Dunphy et al. [39] found that calcification found on CT and 18F-FDG uptake rarely occur simultaneously within a vessel. This provides further rationale for the use of joint PET-CT as a diagnostic tool for GCA in future research.

Another problem with much of the pre-existing research in this field is that GCA is diagnosed inconsistently, based on either clinical criteria, a positive temporal artery biopsy or both. Because GCA shows significant clinical overlap with Takayasu's arteritis and PMR, arbitrary stratification of patients in one of these groups is to some degree unavoidable. However, we argue that further research would significantly benefit from selection of patients with consistently defined GCA. As positive biopsies are currently the most accurate test, disregarding PET, we propose the exclusive selection of patients with positive temporal artery biopsies who fulfil the ACR-criteria for GCA in future research. These ACR-criteria are displayed in table 2.[40]

As a direct consequence of the overlap between GCA and other rheumatic diseases, these disease entities are often pooled in analyses investigating the efficacy of PET in large vessel vasculitis. In our opinion, a disease-specific targeted approach is more desirable because it allows for the design of more accurate diagnostic protocols. In order to make our meta-analysis as accurate as possible, we excluded studies with heterogeneous cohorts, i.e. cohorts consisting of patients with multiple types of vasculitis. By doing so, we achieved consistently low heterogeneity in our analysis. With increasing understanding of the underlying mechanisms and pathology of these diseases, we expect more specific research to be available in the near future.

Table 2 - 1990 ACR criteria for the diagnosis of GCA.

1. Age at onset 50 years or more
2. Newly developed (localized) headache
3. Tenderness of temporal artery or decreased pulse
4. ESR greater than or equal to 50 mm/hr
5. Temporal artery biopsy showing vasculitis

A patient is considered to have GCA if three of these five criteria are met.

Another point of note is that a considerable number of studies include patients who receive corticosteroid therapy during their participation in the study. As demonstrated by Walter et al. [32], the sensitivity and specificity of PET directly correlate with the degree of active inflammation (ESR/CRP) in a patient, with higher accuracy achieved at more active inflammation. Therefore, in clinical practice, PET might reach higher sensitivity because patients not yet on treatment will have highly active inflammation.

Furthermore, many studies include only small cohort of patients, contain poorly matched or absent control groups and are retrospective in design. The consequence of such a design is that ideally only patients who have positive biopsies are studied. Whether there is a difference between the biopsy positive and negative GCA patients in terms of the development of extracranial manifestations is unknown and difficult to investigate. Future research would benefit from larger prospective, randomised trials with accurately matched controls.

With continuing improvement in radiation dosage, image quality and scan time, we expect the sensitivity and specificity of PET to rise even further in the nearby future. A breakthrough in medical imaging was the introduction of the hybrid PET-CT scan. An important disadvantage of PET-scans is that anatomical landmarks are very difficult or impossible to recognise. The joint use of PET and CT can overcome this obstacle, but CT examination can also be used for correction of attenuation on PET images. PET-CT is commonly used in oncology, especially in staging lung cancer and lymphomas.[41,42] Hybrid PET-CT could potentially provide higher diagnostic accuracy that PET alone in the diagnosis of GCA. However, using both imaging techniques could lead to a significant increase in radiation dose. Research is currently being undertaken on how to counteract this disadvantage. Rodríguez-Vigil et al. have reported that the use of low-dose CT is possible without compromising image quality.[43]

Conclusion

After consideration of the results of our literature review and meta-analysis, we conclude that PET cannot replace temporal artery biopsy as a diagnostic modality in GCA at the present time. However, when considering GCA in patients with a negative biopsy, PET may provide a valuable addition because of its ability to visualise extracranial involvement. In our meta-analysis, we found that PET has a sensitivity of 85%, a specificity of 91%, a positive likelihood ratio of 7.18 and a negative likelihood ratio of 0.19 for diagnosing GCA. These values will most likely not be directly applicable in clinical situations, because the exact accuracy of this diagnostic modality will vary with the circumstances in which it is used. PET will achieve a higher accuracy in patients with highly active inflammation (high ESR/CRP levels) and extensive extracranial inflammation, but lower accuracy in those patients who receive immunosuppressive treatment (such as corticosteroids). The diagnostic accuracy of PET could be improved further by the development of standardised scoring systems and the use of joint PET-CT. However, our meta-analysis proves that when used in the right circumstances, PET is a very accurate diagnostic modality when considering GCA in clinical practice.

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