Diagnostic yield of FDG-PET/CT in fever of unknown origin: a systematic review, meta-analysis, and Delphi exercise

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AIM: To perform a systematic review, meta-analysis and Delphi exercise to evaluate diagnostic yield of combined 2-[\textsuperscript{18}F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography and computed tomography (FDG-PET/CT) in fever of unknown origin (FUO).

MATERIALS AND METHODS: Four databases were searched for studies of FDG-PET/CT in FUO 1/1/2000–1/12/2015. Exclusions were non-English language, case reports, non-standard FDG radiotracer, and significant missing data. Quality was assessed by two authors independently using a standardised tool. Pooled diagnostic yield was calculated using a random-effects model. An iterative electronic and face-to-face Delphi exercise generated interspecialty consensus.

RESULTS: Pooled diagnostic yield was 56% (95% confidence interval [CI]: 50–61%, $I^2=61\%$) from 18 studies and 905 patients. Only five studies reported results of previous imaging, and subgroup analysis estimated diagnostic yield beyond conventional CT at 32% (95% CI: 22–44%; $I^2=66\%$). Consensus was established that FDG-PET/CT is increasingly available with an emerging role, but there is prevailing variability in practice.

CONCLUSION: There is insufficient evidence to support the value of FDG-PET/CT in investigative algorithms of FUO. A paradigm shift in research is needed, involving prospective studies recruiting at diagnosis of FUO, with updated case definitions and hard outcome measures. Although these studies will be a significant undertaking with multicentre collaboration, their completion is vital for balancing both radiation exposure and costs against the possible benefits of utilising FDG-PET/CT.

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Introduction

Fever as an isolated clinical presentation has challenged clinicians for decades.\(^1\)\(^2\) In 1961 Petersdorf and Beeson provided a case definition for “fever (or pyrexia) of unknown origin”: (1) a body temperature >38.3°C; (2) on several occasions; with (3) a duration of illness of at least 3 weeks; and (4) no diagnosis within 1 week of hospital admission.\(^2\)\(^3\)\(^4\) Fifty years on, definitions of FUO and the spectrum of aetiologies have evolved; however, the diagnostic challenges remain.\(^4\) FUO represents an estimated 2.9% of hospital admissions, with morbidity associated with prolonged hospital stay, repeated cycles of invasive investigations, presumptive treatment, mortality rates between 12–35%, and cost implications.\(^5\)

Combined 2-[\(^{18}\)F]-fluoro-2-deoxy-D-glucose (FDG) positron-emission tomography and computed tomography (PET/CT) emerged at the end of the 20th century as an amalgamation between functional and conventional anatomical imaging.\(^6\) Its role in oncological staging has been well-defined; however, there is less clarity in other specialities.\(^7\) Specifically, in the investigation of FUO, the role of FDG-PET/CT in clinical practice and diagnostic algorithms is inconsistent and unestablished. Existing guidelines suggest that FDG-PET/CT may be used where conventional investigations have not revealed a source.\(^8\)

FDG-PET/CT is not associated with nephrotoxicity, and standard protocols expose patients to less radiation than a conventional CT. An average FDG-PET/CT scan exposes a patient to 15 mSv radiation, approximately 5–6 years background radiation, rather than 20–25 mSv in a contrast-enhanced chest–abdomen–pelvis CT. Other advantages include imaging areas (e.g., head and neck, extremities) that are beyond the range of most CT scans used in this context, and detection of vascular and truncal musculoskeletal inflammation for which cross-sectional contrast-enhanced CT imaging is insensitive.\(^9\) The main caveats are cost and accessibility, FDG-PET/CT costing £800, compared to £250 for a contrast-enhanced chest–abdomen–pelvis CT; however, this could easily be remunerated by earlier definitive treatment associated with additional diagnostic sensitivity. A marginally reduced length of inpatient stay could mitigate the cost, with an average £400 for one night of hospital admission.\(^10\)

Current literature evaluating the role of FDG-PET/CT in FUO is based on observational data involving small samples, outdated case definitions, and poor generalisability. Outcomes reported by existing meta-analyses focus on sensitivity of FDG-PET/CT in FUO.\(^11\)\(^12\) Sensitivity refers to the proportion of cases with a diagnosis to explain the FUO for which FDG-PET/CT contributed to the diagnosis, or A/(A+B) (Table 1). This is statistically inappropriate as there is no reference standard for the investigation of FUO to enable estimates of diagnostic accuracy.\(^13\) In comparison, diagnostic yield provides a more suitable outcome measure, calculated as the proportion of all FDG-PET/CT examinations (both normal and abnormal) that contribute to the diagnosis of FUO, A/(A+B+C+D) (Table 1).\(^14\) Strikingly, there has been limited analysis of diagnostic yield of FDG-PET/CT beyond that of conventional CT. Further, previous meta-analyses have not studied individual patient data.

The present study was an up-to-date meta-analysis of the diagnostic yield of FDG-PET/CT in all patients with FUO. Secondary outcomes included the proportion with an abnormal FDG-PET/CT, final diagnosis, false-positive results, and mortality. The results of the meta-analysis were used to inform two rounds of a Delphi survey and a half-day meeting, to develop a consensus on the current knowledge on the role of FDG-PET/CT in FUO and inform future research.

Materials and methods

Systematic review and meta-analysis

The protocol was registered prospectively with PROSPERO, an online international database of systematic reviews (study ID CRD42016032696). It adhered to PRISMA guidelines.\(^3\)\(^6\) QUADAS-2, STROBE, Cochrane guidelines, and MOOSE guidelines were also utilised.\(^15\)\(^–\)\(^18\)

Inclusion and exclusion criteria

All patients were included irrespective of age, comorbidities, or whether patients were immunocompromised. Inclusion criteria for FDG-PET/CT protocols were not defined, provided they involved a standard FDG radiotracer. Exclusion criteria were case reports, significant missing data such that the primary outcome could not be calculated and non-English studies.

Search strategy

Electronic searches were performed 1/12/15 in MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. All subheadings were included. Hand-searching of references was performed for included studies and identification of unpublished work was attempted by contacting experts and reviewing conference abstracts. MESH terms used for Ovid Medline were: (‘Tomography Positron-Emission’ OR ‘Fluorodeoxyglucose F18’) AND (‘Fever’ exploded). For EMBASE the terms were: (‘Positron Emission Tomography’ OR ‘Fluorodeoxyglucose F18’) AND (‘Fever’ exploded). Keyword searches were undertaken for: (‘Positron Emission’ OR ‘PET’ OR ‘fluorodeoxyglucose’ OR ‘labeled glucose’ OR ‘18fluorodeoxyglucose’ OR ‘fdg’ OR

Table 1

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<thead>
<tr>
<th>Two-by-two table categorising possible study outcomes.</th>
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<tr>
<td>[A] True positives: Patients with an abnormal FDG-PET/CT that contributed to diagnosing the cause of the FUO.</td>
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<tr>
<td>[B] False negatives: Patients with a normal FDG-PET/CT that received a diagnosis by other means.</td>
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<tr>
<td>[C] False positives: Patients with an abnormal FDG-PET/CT that did not contribute to diagnosing the cause of the FUO.</td>
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<tr>
<td>[D] True negatives: Patients with a normal FDG-PET/CT that remained undiagnosed after investigation or follow-up.</td>
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