

## Supplement

### Technical Aspects and Specific Protocols for PET and CECT Components

- For the CUP scenario especially for primary evaluation and staging, all scans should be performed with triphasic CECT parameters unless contraindicated (renal failure, severe known allergy).
- Adequate hydration is important to ensure a sufficiently prompt excretion of FDG through the urine and reduce FDG-associated artifacts and for radiation safety reasons. Patients should void immediately before the PET/CT examination to reduce bladder activity.
- During the injection of FDG and the subsequent uptake phase, the patient should remain seated or recumbent and silent to minimize muscle uptake.
- Routinely the patient should be positioned with the arms elevated and supported above the head to avoid beam-hardening artifacts in the abdominal and pelvic regions as well as artifacts caused by truncation of the measured field of view (FOV). It is advised to acquire the head and neck part with the arms down and then apex of the lung through the mid-thigh with the arms up, especially when neck disease is suspected.
- The scan should cover the vertex to the mid-thigh. Extended total-body examinations are performed in patients with tumors that show a high probability of primary lesion in distant sites like melanoma or mesenchymal tumors. We recommend this routine extended imaging only in clinically suspected or symptomatic lower limb lesions.
- The patient should be supine with their arms above their head scout image to acquire from vertex to mid-thigh.
- Craniocaudal triphasic CECT with tube potential of 110 to 120 kVp and current of variable mAs (100–240 mAs) as per weight, age, and automatic tube current modulation.
- The slice thickness should be less than 5 mm (1.5–2 mm is recommended), and 16 or greater slice multidetector CT scanner is recommended.
- Iodinated nonionic water-soluble contrast agents like Iohexol (OMNIPAQUE) and Iodixanol (VISIPAQUE) are widely used owing to their proven safety and ease of usability.
- Total amount of contrast injected is also to be decided upon the weight of the patient (commonly 75–90 kg individual requires 100–120 cc of contrast agent).
- Flow rate of 3 to 5 mL/s is to be achieved (should not be less than 2.5 mL/s) with an adequate bore-sized IV (at least 20G) cannula and programmable fluid injector.

Phases acquired as—late arterial phase 15 to 30 seconds post-bolus trigger (35–45 s after injection) followed by portal venous phase 60 to 75 seconds postinjection (independent of arterial timing), and delayed phase at 2 to 5 minutes. The region of interest for the arterial phase can be extended in head–neck and chest regions as per individual case requirements.

- Positive iodinated oral contrasts such as diatrizoate meglumine and diatrizoate sodium solution USP

(ANGIOGRAFIN/UROGRAFIN/GASTROGRAFIN) (20 mL diluted in 950–1,000 mL of plain water given 30–40 minutes before acquisition) should be used to distend bowel loops adequately.

- This is to be followed by PET acquisition in the caudocranial orientation. The acquisition time is variable from a few seconds to 5 minutes per bed position depending upon the injected activity, patient weight, axial FOV, and detector type. It takes approximately 10 to 15 minutes to image a normal adult with present commonly used time-of-flight scanners.
- Delayed nephrogenic phase if necessary can be suitably taken directly after PET acquisition.
- The exact choice of imaging protocol strongly depends on the clinical symptomatology for every single case. Pediatric studies require special attention. For the optimization of FDG PET/CT studies, dose reduction techniques should be considered.
- Regional dual time-point imaging/delayed non-contrast-enhanced imaging is recommended in case of initial indeterminate uptake after 3 hours.
- Few dedicated regional protocols are advised for some scenarios as:
  - Regional acquisition with puffed cheek (patient inflates cheeks, purses lips, and holds their breath) PET with regional thin sliced dedicated CT for suspected head–neck (oral) malignancy. Multiple organs with high physiological FDG uptake such as tonsils are to be screened keenly if needed with delayed imaging.
  - Regional acquisition with modified Valsalva technique or “eee” phonation is recommended in suspected tumors of the pharynx and larynx.
  - On table plain water/oral contrast (250–400 mL) for adequate esophageal and stomach visualization for the suspected gastroesophageal lesion.
  - Dedicated end-inspiratory noncontrast-enhanced high-resolution CT chest is advised in case of suspected lung primary, especially in cases with indeterminate mediastinal lymphadenopathy and chest symptoms.
  - Urinary bladder should be catheterized in suspected pelvic/bladder lesions and when the patient specifically has voiding difficulties.
  - Adequate bowel preparation, if needed enema with rectal contrast, is also recommended in suspected distal large bowel lesions.

These special protocols can be suitably added to the standard protocol and done at the time of delayed imaging after initial indeterminate distal large bowel findings.

### Synoptic Reporting Formats for PET-CECT in Carcinoma of Unknown Primary

- Patient Identification:
- Age/Sex:
- Clinical history with Indication: brief symptomatology, labs, and histology if any.

For primary disease evaluation/staging/response, recurrence evaluation.

### Technique/Procedure

It is composed of vital information such as radiopharmaceutical name, administered activity, route of administration, and uptake time (i.e., time from injection to imaging), blood glucose at the time of  $^{18}\text{F}$ -FDG injection, actual axial coverage, PET instrument parameters and particulars, and CT parameters (i.e., kVp and mAs). If contrast was used, the type and volume of contrast agent.

### Findings

“Order of Importance” style is recommended to be followed.

Findings are described as per their importance to the clinical care of the patient, e.g., report as per TNM staging classification for a particular tumor in question.

Standardized radiology lexicon with location, extent, and intensity of abnormal radiotracer activity reported with anatomic correlation with the concurrent CT scan.

Provide approximate size measurements for nodules and masses, either as a single transaxial diameter or in two or three orthogonal directions.

The intensity of  $^{18}\text{F}$ -FDG uptake within a lesion is to be reported using qualitative (e.g., mild, moderate, or intense) terminology and also using semiquantitative measures such as the  $\text{SUV}_{\text{max}}/\text{SUV}_{\text{peak}}/\text{SUV}_{\text{mean}}$  whenever possible.

It is also recommended to mention sites of physiological tracer uptake and other nonrelevant but tracer areas with tracer uptake.

### Impression

This should be a brief and concise interpretation of findings, their differentials, and likelihood with a short discussion: characteristic of current findings, their clinical relevance, and answers to the specific clinical questions by the referring physician. In response evaluation scan, both the metabolic response and anatomic response may be reported in the impression with the possibly standardized system (RECIST/PERCIST). Further comments upon the use of additional imaging/pathologic modality and follow-up study should be given when necessary. Other urgent or emergency findings (e.g., pneumothorax, intracranial hemorrhage) should be communicated rapidly to referring physicians, and the date, time, and means of communication should be documented at the end of the imaging report.<sup>13,42</sup>

## Example Report

### Clinical History with Indication

Presented with left-sided neck swelling with no obvious abnormality on local clinical examination, reported having

SCC on USG-guided FNAC, for further primary disease evaluation and staging.

### Technique/Procedure

$^{18}\text{F}$  FDG, 192 MBq (5.2 mCi) intravenously, via left antecubital vein, blood glucose at time of  $^{18}\text{F}$ -FDG injection: 95 mg/dL (5.3 mmol/L).

Time from  $^{18}\text{F}$ -FDG injection to scan: 65 minutes.

PET/CT images were acquired from the vertex through the upper thighs; CT images were acquired at a 2-mm slice thickness using a tube current of 120 kVp and 200 mA. 80 mL of Iohexol (Omnipaque) was used as the intravenous contrast agent at the rate of 3 mL/s.

### Findings

Intense FDG uptake is noted in heterogeneously enhancing soft tissue density lesion along left-sided tonsillar fossa measuring approximately mild FDG uptake seen in the lytic destructive soft tissue lesion, measuring around  $1.2 \times 0.9$  cm with  $\text{SUV}_{\text{max}}$  of 6.5.

Similarly, FDG uptake is noted along contrast-enhancing left-sided cervical nodes as:

Group of left-sided level II nodes, largest measuring  $1.8 \times 1.1$  cm with  $\text{SUV}_{\text{max}}$  of 5.2.

Group of left-sided level Ib nodes, largest measuring  $1.5 \times 1.1$  cm with  $\text{SUV}_{\text{max}}$  of 5.5.

Few non-FDG concentrating tiny level V nodes are noted with preserved fatty hilum—appears reactive.

Non-FDG concentrating fibro-cavitary changes noted in apical segments of bilateral lungs—appear to as a postinfective sequel.

Physiological uptake of the tracer is noted in the brain, vocal cords, myocardium, liver, spleen, renal pelvicalyceal systems, urinary bladder, and the gut. The rest of the whole-body survey shows unremarkable tracer distribution.

### Impression

In this case of left-sided neck nodal swelling under evaluation:

Intensely FDG concentrating lesion in left tonsillar fossa as described is suspicious for the site of primary disease, however, needs further histopathological correlation, similarly FDG avid left-sided neck nodes appear metastatic—sites of regional metastases, no other FDG concentrating suspicious lesion is noted in visualized rest body in limits of the present scan.