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Prevalence and clinical impact of incidental findings on the unenhanced CT images of PET/CT scan in patients with multiple myeloma: the value of radiological reporting in the multimodal hybrid imaging

N. MAGGIALETTI[1], C. FERRARI[2], A.G. NAPPI[2], D. RUBINI[2], A.R. PISANI[2], C. MINOIA[3], V. GRANATA[4], M. MOSCHETTA[5], A. STABILE IANORA AMATO[6], G. RUBINI[2]

[1]Department of Basic Medical Science, Neuroscience, and Sense Organs, University of Bari Aldo Moro, Bari, Italy
[2]Interdisciplinary Department of Medicine – Section of Nuclear Medicine, University of Bari Aldo Moro, Bari, Italy (A.G.N.)
[3]Hematology Unit – IRCCS Istituto Tumori "Giovanni Paolo II", Bari, Italy
[4]Division of Radiology, Istituto Nazionale Tumori IRCCS Fondazione Pascale-IRCCS di Napoli, Naples, Italy
[5]DETO, Department of Emergency and Organ Transplantations, Breast Care Unit, Aldo Moro University of Bari Medical School, Bari, Italy
[6]Interdisciplinary Department of Medicine – Section of Diagnostic Imaging, University Hospital Policlinico of Bari Medical School, Bari, Italy

Abstract. – OBJECTIVE: In the hybrid Positron Emission Tomography/Computed Tomography (PET/CT) method, the functional evaluation is integrated with the morphological information provided by co-registered CT, still performed for attenuation correction and lesion localization. However, co-registered CT images could provide additional diagnostic information that PET alone could underestimate. To optimize the diagnostic potential of this hybrid examination, we evaluated the prevalence and the clinical significance of incidental findings detected on co-registered CT images in a cohort of multiple myeloma (MM) patients.

PATIENTS AND METHODS: We evaluated 112 MM patients (mean age 65.8 y), who underwent [^{18}F]FDG-PET/CT during their regular workup. All co-registered CT images were retrospectively reviewed by two expert radiologists and each non-myelomatous incidental finding (nM-IF) was collected and clinically graded according to a nM-IF Reporting and Data System (nM-RADS). In addition, nM-IFs were classified according to anatomic localization (skull, lung, mediastinum, abdomen, breast, gastrointestinal, genitourinary and cardiovascular system and muscle/soft tissue).

RESULTS: 163 nM-IFs were detected in 94/112 patients (83.9%) (mean value: 1.5 IFs per patient). The most interested anatomic districts were the lung (n=33; 20.2%), genitourinary (n=33; 20.2%) and gastrointestinal (n=30; 18.4%) systems. Focusing on the clinically significant findings (nM3+nM4), 92/163 (56.4%) IFs could have been required further investigations, of which 38/163 (23.3%) were potentially important and detected in 33/112 (29.5%) patients.

CONCLUSIONS: The high percentage of potentially clinically significant IFs detected in MM patients emphasizes that co-registered CT images hold precious information often missed. Giving more relevance to co-registered CT with tailored acquisition and reconstruction protocols and dedicated reporting could optimize the potentiality of this multimodality imaging method with impact on clinical management.

Key Words:
[^{18}F]FDG-PET/CT, Incidental findings, Multimodality imaging, Unenhanced CT, Co-registered CT.

Introduction

Over twenty years from the introduction of the first Positron Emission Tomography/Computed Tomography (PET/CT) integrated scanner prototype, this multimodal imaging method has revolutionized patient's care and clinical management.

Thanks to the integration of functional and morphological information, it could offer the best

Corresponding Author: Pisani Antonio Rosario, MD; e-mail: apisani71@libero.it

of both modalities to enhance the overall diagnostic accuracy[1].

However, nowadays there is still a lot to discover about the potential of this complex method.

Literature[2] already reports that hybrid imaging improves lesion detectability, localization and characterization, by comparing PET/CT results with those from separate PET and CT exams. Nevertheless, the added diagnostic and clinical value of the low-dose CT co-registered to PET (co-registered CT) remains underestimated. Osman et al[3] analyzed a heterogeneous cohort of cancer patients, emphasizing the clinical and diagnostic importance of the co-registered CT morphological information. It proved to be not only complementary to PET but also with its own diagnostic value, especially for lesion that PET alone might fail to detect.

A possible added role of co-registered CT could be the detection of incidental findings (IFs), defined as an "incidentally mass or lesion, detected by an imaging examination, performed for an unrelated reason"[4]. The IFs detection could impact the therapeutic iter of cancer patients, particularly for those undergoing a surgical procedure or chemotherapy. The American College of Radiology (ACR) IF Committee has published several white papers outlining imaging and clinical criteria for IFs management. The so-called Reporting and Data Systems (RADS) represent guidelines for the evaluation and interpretation of imaging studies, specific for each modality and technique, also in relation to IFs[5].

Literature data regarding the prevalence and the potential clinical relevance of IFs detected on co-registered CT are still few. Pinilla et al[6] compared the performance of PET/CT by using two different co-registered CT protocols. In this study, the authors found no significant improvement in PET accuracy between low-dose CT and full-dose enhanced CT in the initial staging of lymphoma, but full-dose enhanced CT detected relevant IFs (5.9%) missed at low-dose CT.

Our group previously investigated the potential diagnostic value of co-registered CT, evaluating a cohort of multiple myeloma (MM) patients in different stages of disease[7]. In this setting, co-registered CT showed similar performance compared to the whole-body low dose CT standard protocol in bone disease evaluation. These results led us to suggest using [^{18}F]Fluorodeoxyglucose PET/CT ([^{18}F]FDG-PET/CT) as the only imaging method, speculating an impact on patient compliance, health care spending and especially radiation exposure[7]. The importance of co-registered CT bone findings, reported by radiologists, was already emphasized by the International Myeloma Working Group (IMWG) to fulfill CRAB criteria[8].

Having a prevalent bone involvement, MM could represent an ideal model to investigate the added diagnostic value of co-registered CT through the detection of IFs not related to hematological neoplasm.

Starting from these premises, the present study aims to investigate the diagnostic role of co-registered CT in MM patients, by evaluating: i) the prevalence of non-myelomatous IFs (nM-IFs), detected by expert radiologists, and ii) the clinical significance of nM-IFs in patients management.

Patients and Methods

Population Characteristics

A homogeneous cohort of 112 MM patients (67 men and 45 women; mean age of 65.8 years, range 25-87) was included in the study. All patients underwent [^{18}F]FDG-PET/CT for disease staging (n=28) or treatment response assessment (n=84) from January 2019 to March 2021. None of the patients had a diagnosis of known secondary cancer.

The present study was performed following the Declaration of Helsinki and approved by the local Ethics Committee (Prot. n. 828 CE, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy). All patients signed informed consent for the scientific use of medical data.

PET and CT Protocols

All [^{18}F]FDG-PET/CT scans were performed following the international guidelines of the European Association of Nuclear Medicine[9]. Patients underwent [^{18}F]FDG-PET/CT after at least 6 h of fasting, adequate hydration and capillary blood glucose level lower than 160 mg/ml. Images acquisition was obtained 45-60 minutes after the intravenous injection of 2.5 MBq/kg of [^{18}F] FDG, by using a combined PET/CT scanner Discovery™ IQ (GE, Healthcare Technologies, Milwaukee, WI, USA) that integrated a 3D scanner PET with multidetector helical 16-slice CT scanner (light speed plus).

The PET acquisition was obtained in cranial-caudal direction, from the skull to mid-thigh, in supine decubitus with arms placed alongside the body to include them in the field of view (FOV) and for an optimal image reading and interpre-

tation. PET was reconstructed with a matrix of 256x256, ordered subset expectation maximum iterative reconstruction algorithm (four iterations, 28 subsets), 8 mm Gaussian filter, and 70 cm FOV.

The co-registered CT acquisition was performed immediately before PET scanning and used for attenuation correction and anatomical localization. In literature, different CT protocol co-registered to PET are reported[7].

In the present study, a low dose co-registered CT was performed, minimizing radiation dose exposure according to ALARA principle and the European Directive legislation 97/43/EURATOM, but ensuring good PET image quality. All co-registered CT were acquired with 3.75 slice thickness. A lower acquisition thickness was not possible to guarantee a good attenuation correction for PET imaging. Detailed CT acquisition parameters are reported in Table I.

Table I. CT acquisition parameters.

CT Scan Parameters	
Tube voltage (kv)	120
Noise index	28.5
Pitch	0.938
Range	15-350 mA
FOV/matrix	500 mm/512
Detector configuration	16x1.25
Slice thickness (mm)	3.75

Images Interpretation and Data Analysis

Co-registered CT images were retrospectively evaluated by two expert radiologists (N.M. and M.M.), double blinded and blinded about possible comorbidities and PET results. Any discrepancies were reviewed by both readers for consensus. All exams were reviewed on a dedicated workstation with MPR/VR reconstruction (Advantage Workstation; GE Healthcare Technologies, Milwaukee, Wisconsin, USA).

All findings not related to MM disease were included in the analysis and defined as non-myelomatous IFs (nM-IFs)[10].

Exclusion criteria for nM-IFs were: i) osseous findings (e.g., typical degenerative osteoarthritis) for difficulty in differentiating them from myelomatous findings; ii) extramedullary MM localization, basing on CT features; and iii) age-related findings (for example, vasosclerosis), considered paraphysiological[11].

The clinical relevance of each nM-IF was graded by using a 5-points score system ranging from nM0 to nM4, with increasing score according to nM-IF clinical impact, that we named nM-RADS (Table II). This classification was inspired by previous ACR "RADS"[12-15], taking into account specific radiological criteria, as follows: i) dimensional criteria for vascular dilatation and solid lesions (e.g., pulmonary nodule or pleural thickening <1 cm were classified as nM3, while ≥1 cm as nM4; as well as mediastinal lymph nodes <2 cm as nM2, ≥2 cm as nM3), and ii) qualitative criteria by analyzing CT texture and density features.

In addition, each nM-IF was categorized according to anatomic localization: skull, lung, mediastinum, breast, abdomen, gastrointestinal, genitourinary, cardiovascular system, and muscle/soft tissues.

Results

A total of 163 nM-IFs were detected in 94/112 patients (83.9%), with a mean value of 1.5 nM-IFs for patients. According to nM-RADS, IFs were classified as follows: 4/163 (2.5%) nM1, 67/163 (41.1%) nM2, 54/163 (33.1%) nM3, and 38/163 (23.3%) nM4. No exam was limited or compromised by artefact (nM0=0).

Among 4 nM1-IFs, 1 was detected in abdomen (accessory spleen), 1 in gastrointestinal system (gastric diverticulum), 1 in genitourinary system (horseshoe kidney), and 1 in cardiovascular system (retroaortic left renal vein).

Out of 67 nM2-IFs: 21% were in the skull (13 sinusitis, 1 leptomeningeal cyst), 9% in lung (1 pleural thickening <1 cm, 1 fibrosclerosis, 3 low-grade emphysema, 1 calcific pulmonary nodule),

Table II. Non-Myelomatous Reporting and Data System (nM-RADS) classification.

nM-RADS	
nM0	Limited exam (compromised by artefact)
nM1	Normal exam or anatomic variant
nM2	Clinically unimportant finding for which it is not indicated work-up
nM3	Likely unimportant and incompletely characterized finding for which further investigations could be indicated
nM4	Potentially important finding for which work-up is indicated

8% in mediastinal region (1 thyroid lobe agenesis, 4 mediastinal adenopathies <2 cm), 5% in abdominal cavity (2 liver cysts, 1 spleen calcification), 10% in gastrointestinal system (4 gastric hernias, 1 duodenal lipoma, 1 aerobilia post-colecistectomy, 1 adenomesenteritis), 28% in genitourinary system (8 renal cysts, 3 kidney stones, 3 adrenal adenomas, 1 uterine fibromatosis, 1 uterine fibromyoma, 1 pelvic floor prolapse, 1 calcific ovarian nodule, 1 kidney shrinkage), and 19% in muscle/soft tissue (6 inguinal hernias, 2 intramuscular lipomas, 2 elastofibromas, 1 crural hernia, 1 umbilical hernia, 1 laparocele).

Out of 54 nM3-IFs: 17% were in lung (2 nodules <1 cm, 2 pneumonia, 2 interstitial lung diseases, 2 pleural effusions, 1 ground-glass opacity), 11% in mediastinal region (5 thyroid nodules, 1 mediastinal adenopathy >2 cm), 2% in abdominal cavity (peritoneal effusion), 35% in gastrointestinal system (15 diverticular diseases, 4 gallstone diseases), 22% in genitourinary system (3 prostatic adenomas, 3 complex renal cysts, 3 ureteral stones, 2 renal angiomyolipomas, 1 irregular uterine cervix thickening), 2% in breast (lipoma), and 11% in cardiovascular system (3 pericardial effusions, 2 abnormal pulmonary artery ectasia, 1 splenic artery aneurysm).

Out of 38 nM4-IFs: 47.4% were in lung (10 interstitial pneumonia, 3 nodule >1 cm, 3 calcified pleural plaques, 2 pleural thickening >1 cm), 23.7% in abdominal cavity (8 liver nodules >1 cm, 1 peritoneal carcinomatosis), 7.9% in gastrointestinal system (1 appendicular mucocele, 1 anal wall thickening, 1 rectal wall thickening), 2.6% in genitourinary system (small renal mass), 2.6% in breast (isodense nodule >1 cm), and 15.8% in cardiovascular system (5 ascending aortic aneurysm ≥4 cm, 1 abdominal aortic aneurysm 5 cm).

Figures 1, 2, 3 and 4 are representative cases of nM-IFs from our sample.

92/163 potentially clinically significant IFs (nM3+nM4) were found in 70/112 (62.5%) patients, among which further diagnostic investigations would be recommended in 33/112 (29.5%) patients.

The distributions and frequencies of nM-IFs and nM3/nM4-IFs according to the anatomic localization are shown in Figure 5 and Table III.

Discussion

Nowadays, PET/CT is routinely used in oncological patients work-up. However, the full value of this hybrid examination and the diagnostic potential of the independent reading of the morphological component is poorly investigated in literature[3,6,16]. Since 2005, Schöder et al[17] emphasized the added diagnostic value of the CT data interpretation, providing incremental diagnostic information that PET alone might miss.

Among several clinical applications, MM represents an oncological disease in which the integrated evaluation of both functional and morphological component would ensure the full use of PET/CT potentialities as recommended by IMWG since 2014[18-21].

As suggested by Surov et al[22], this set of patients with a prevalent skeletal involvement could be an ideal cohort to emphasize the diagnostic potential of the independent interpretation of co-registered CT, through the nM-IFs detection.

In our study, we found a considerable percentage of nM-IFs (83.9%) with a mean value of 1.5 IFs per patient.

According to the anatomical distribution, lung (20.2%) and genitourinary system (20.2%), followed by gastrointestinal one (18.4%), were the most involved. Compared to Surov et al[22], we found a lower mean number of IFs per patient (1.5 *vs.* 3.2). This result was probably due to our decision of not including age-related findings, e.g., vasosclerosis. This consideration could also explain the major involvement of the cardiovascular system (29.2% of all findings) reported by the authors[22]. Conversely, the high number of inflammatory findings, detected in both studies, was probably due to the immunosuppressive state of MM patients. In our sample, 84/112 (75%) patients performed PET/CT for therapy response assessment, after one or more courses of anti-neoplastic treatments and immunomodulatory drugs.

Regarding the clinical relevance, we detected nM3/nM4-IFs in a high percentage of MM patients (62.5%). Among them, 29.5% of patients presented nM4-IFs, more frequently located in the lung (e.g., 10 interstitial pneumonia, 3 calcified pleural plaques), followed by the abdomen (e.g., 8 liver nodules) and the cardiovascular system (e.g., 5 ascending aortic aneurysm).

A much lower percentage of potentially clinically significant IFs (3%) on the co-registered CT was reported by Osman et al[3] in a heterogeneous cohort of cancer patients, and indeterminate renal lesions were the most frequent. This different result may be justified by the lower mean age of the Osman et al[3] population (56.5 y *vs*. 65.8 y), the different cohort features, and especially by the exclusion of small pulmonary nodules as significant findings.

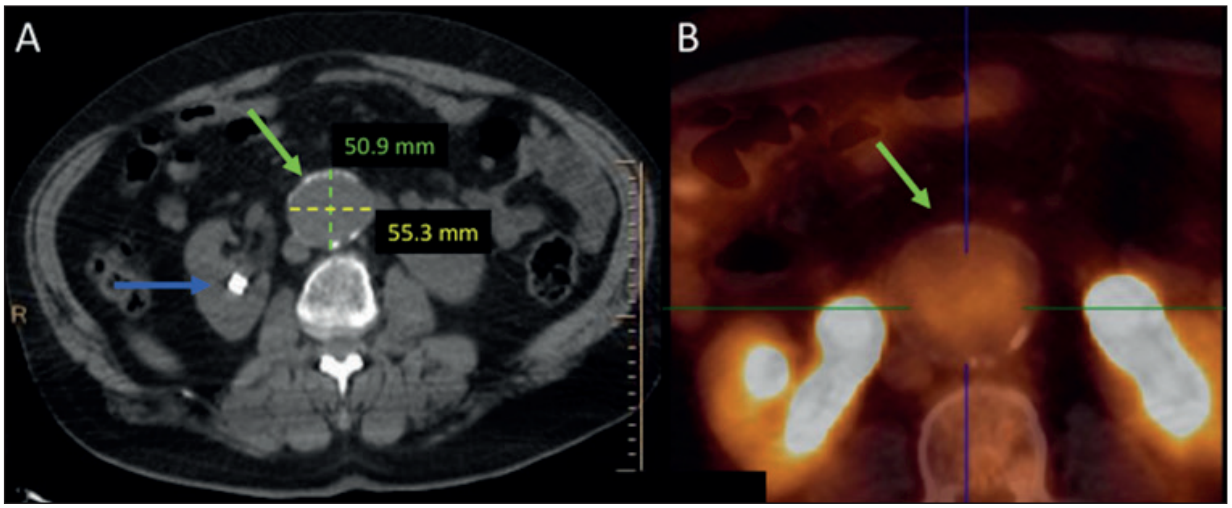

Figure 1. Incidental findings in a 61-year-old multiple myeloma patient who underwent [^{18}F]FDG-PET/CT for post-therapy (chemotherapy and immunosuppressive therapy) restaging. A right kidney stone (blue arrow), classified as nM2-IF, and an aortic aneurysmal dilatation (green arrows), classified as nM4-IF, were detected on (**A**) co-registered CT. **B**, Axial fused PET/CT image.

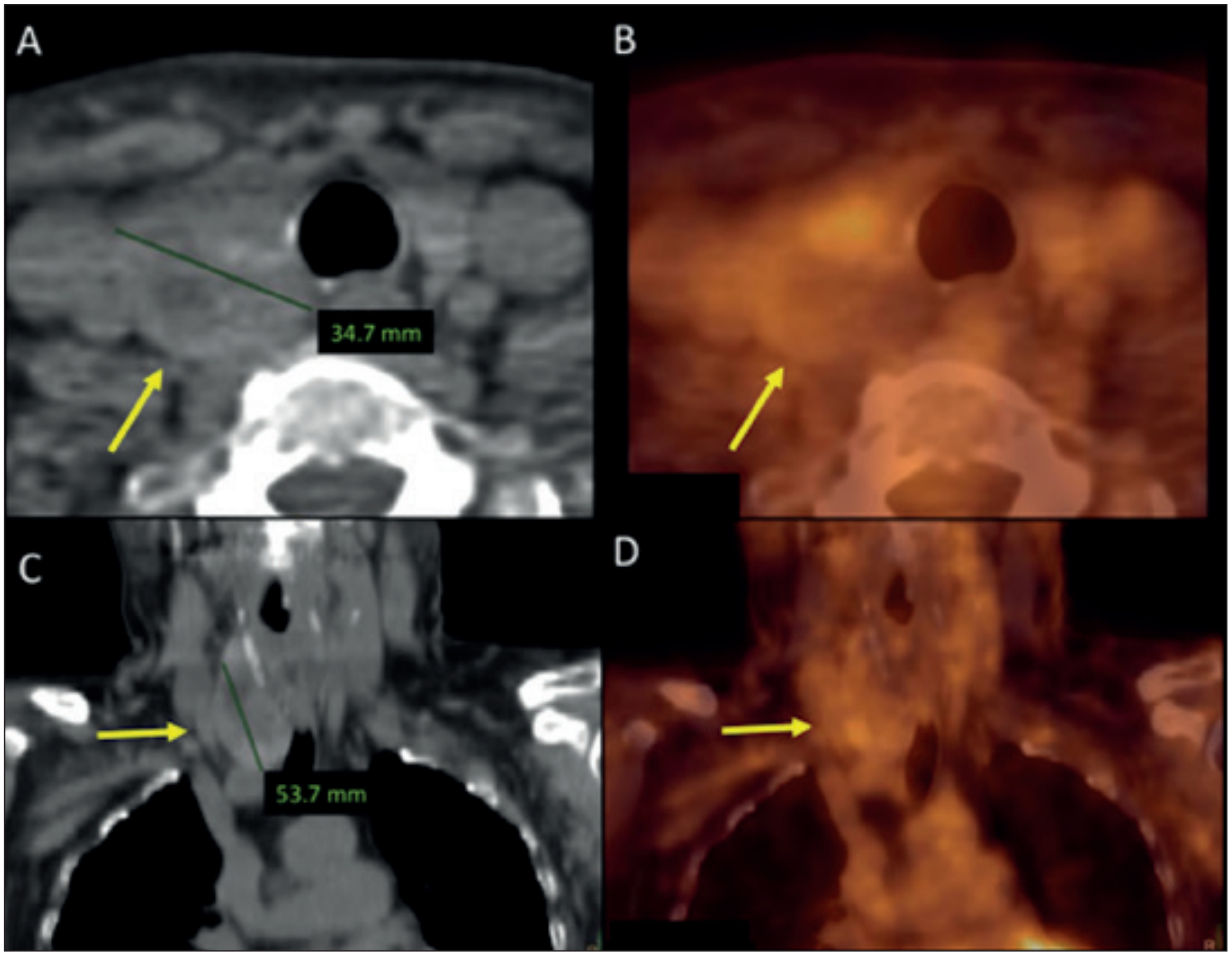

Figure 2. Incidental finding in a 69-year-old multiple myeloma patient who underwent [^{18}F]FDG-FDG PET/CT for post-therapy (chemotherapy and immunosuppressive therapy) restaging. A large right thyroid lobe nodule (53.7x34.7 mm) involving thoracic inlet, classified as nM3-IF (yellow arrows), was detected on co-registered CT (**A**, axial and **C**, coronal reconstructions), which did not show [^{18}F]FDG-uptake on (**B**) axial and (**D**) coronal fused PET/CT images.

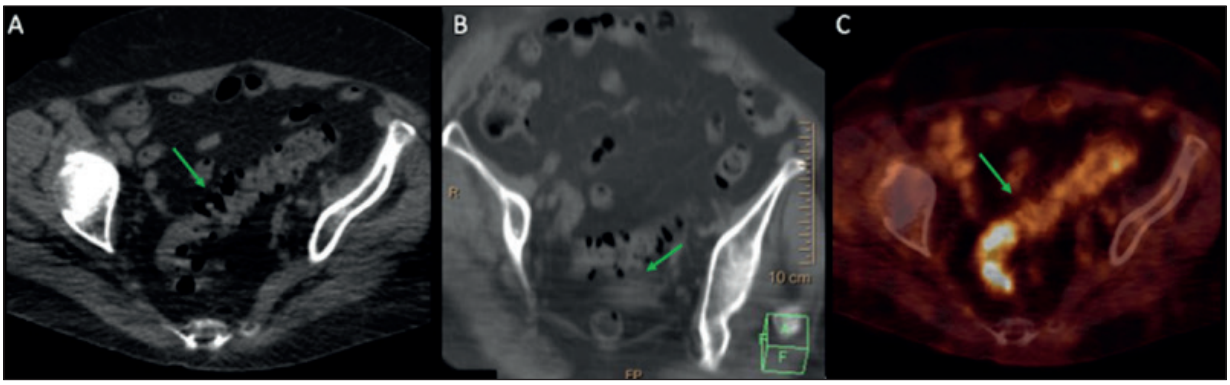

Figure 3. Incidental finding in a 76-year-old multiple myeloma patient who underwent [^{18}F]FDG-PET/CT for post-therapy (chemotherapy, zoledronic acid and immunosuppressive therapy) restaging. Diverticular disease (green arrows) was detected on co-registered CT (**A**, axial and **B**, oblique reconstructions), and classified as nM3-IF, because of a wall thickening, an irregular hyperdensity of perivisceral fat and a small peritoneal effusion were observed. This finding showed mild [^{18}F]FDG-uptake on (**C**) axial fused PET/CT image.

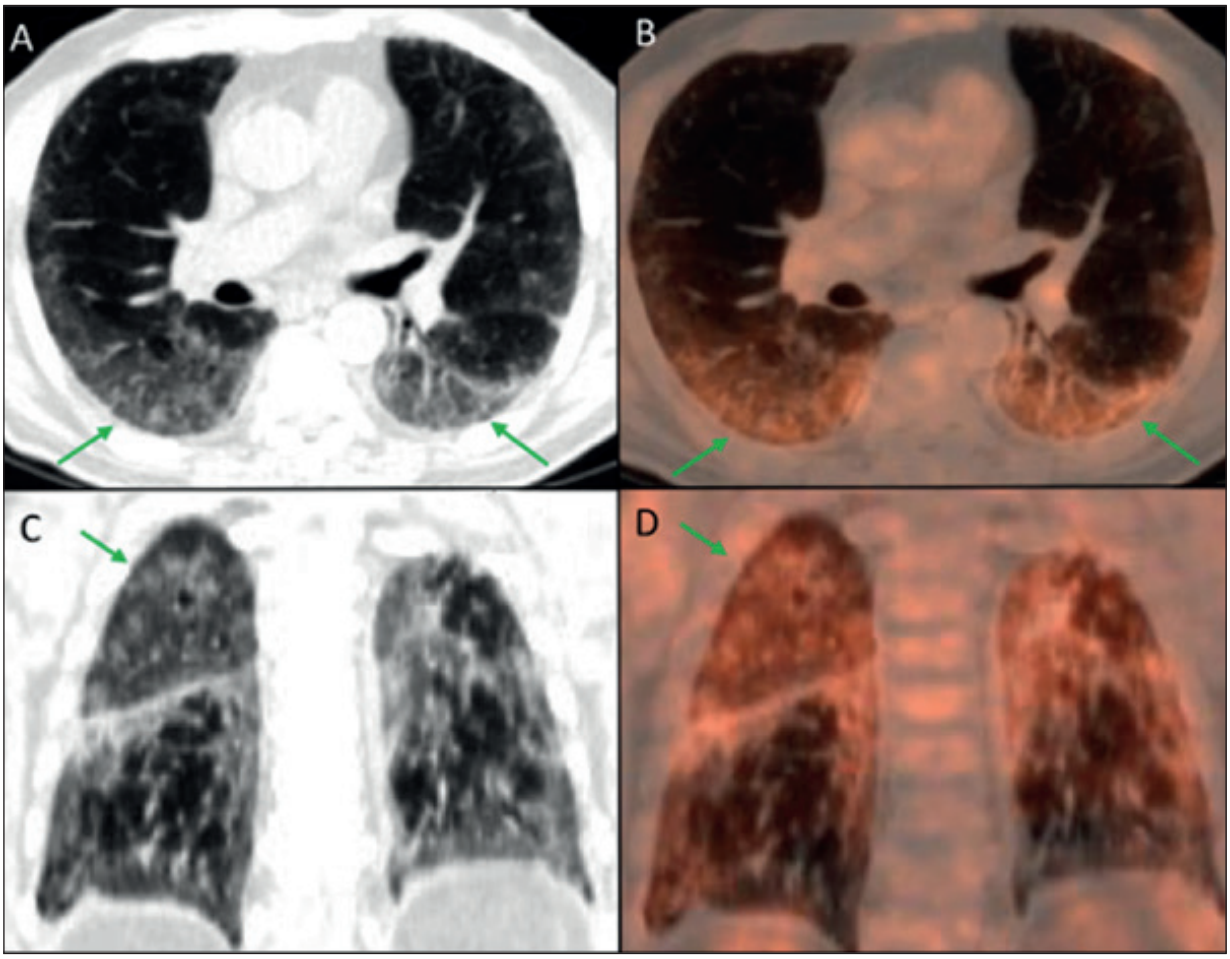

Figure 4. Incidental finding in a 73-year-old multiple myeloma patient who underwent [^{18}F]FDG-PET/CT for staging. Interstitial pneumonia (green arrows), characterized by bilateral ground glass opacities with peripheral distribution, was detected on co-registered CT (**A**, axial and **C**, coronal reconstructions), and classified as nM4-IF, suspicious for COVID-19 infection. This finding showed mild and non-specific increased [^{18}F]FDG-uptake on (**B**) axial and (**D**) coronal fused PET/CT image.

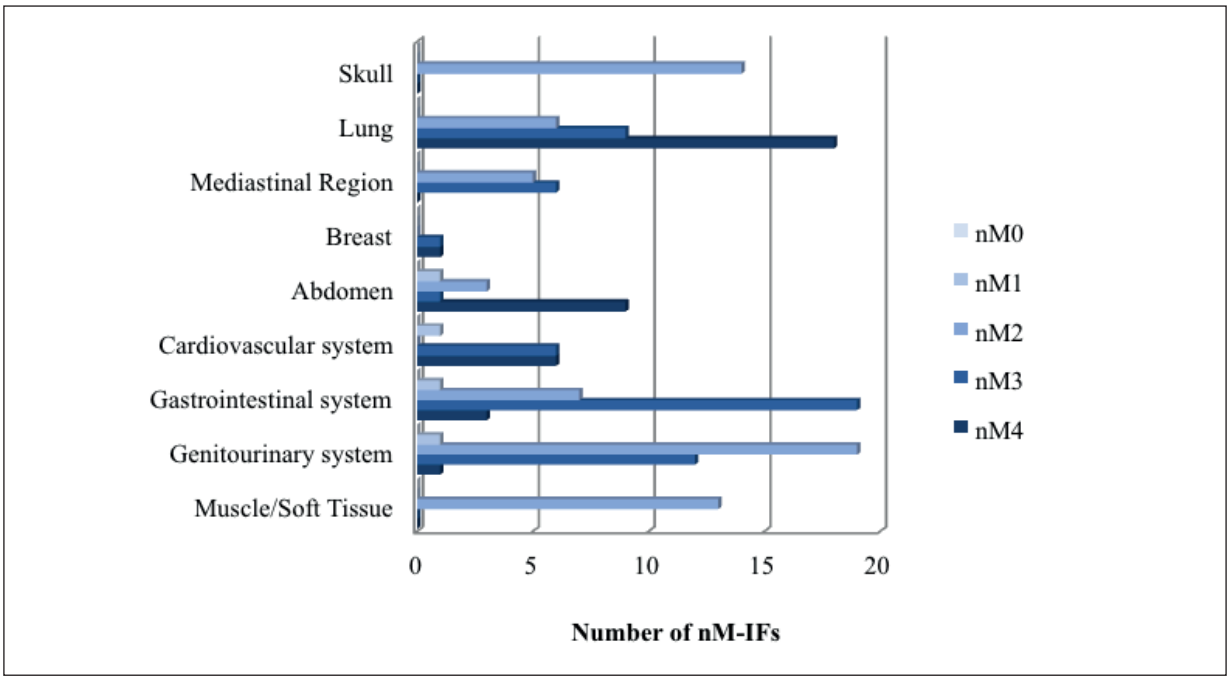

Figure 5. Distribution of nM-IFs according to the anatomical localization.

Of note, the detection of high percentage of clinically relevant IFs in the lung (nM4-IFs=47.4%) deserves an important consideration, in relation to our study recruitment period (January 2019-March 2021). Since February 2020, COVID-19 pandemic is representing a global health emergency with interstitial pneumonia as the most pathognomonic CT finding, suggestive for SARS-CoV-2 infection, both in asymptomatic and paucisymptomatic patients. As expected[23], in our sample 10 interstitial pneumonia were incidentally detected and classified as nM4, requiring an antigen or molecular-based test to confirm infection suspicion. In this scenario, the accurate co-registered CT lung evaluation is highly recommended, considering that the metabolic features of COVID-19 pneumonia could be non-specific. On the other hand, the high number of pulmonary nM4-IFs was also due to the clinical relevance of calcified pleural plaques in our geographic area, since the high incidence of asbestos-related disease following professional/ambiental exposure.

The detection of clinically significant IFs could modify patient's therapeutic iter and prognosis, allowing an early diagnosis and promptly treatment of unknown pathological conditions.

Table III. Anatomical localization of all non-myelomatous incidental findings and of nM3/nM4-IFs.

Anatomic Localization	nM-IFs		nM3-IFs		nM4-IFs	
	n	%	n	%	n	%
Skull	14	8.6	0	-	0	-
Lung	33	20.2	9	16.7	18	47.4
Mediastinal Region	11	6.8	6	11.1	0	-
Breast	2	1.2	1	1.9	1	2.6
Abdomen	14	8.6	1	1.9	9	23.7
Cardiovascular system	13	8.0	6	11.1	6	15.8
Gastrointestinal system	30	18.4	19	35.1	3	7.9
Genitourinary system	33	20.2	12	22.2	1	2.6
Muscle/Soft Tissue	13	8.0	0	-	0	-
Total	163	100	54	100	38	100

Our results demonstrated that co-registered CT holds precious additional information and should be further enhanced with tailored acquisition and reconstruction protocols for each anatomical district by a dedicated radiologist. Particularly, the study of pulmonary IFs could be optimized by the use of respiratory-gated acquisition and dedicated reconstruction. For vascular anomalies[24], the contrast medium during PET/CT exam could allow a better detection of pulmonary artery dilatation, while cardiac gated acquisition could help the ascending aorta diameters evaluation.

It is also not negligible that further investigations to define the IFs nature will lead to an increase of health care costs. However, since we are considering the IFs on hybrid imaging, unnecessary exams may be avoided thanks to the simultaneous assessment of the lesions metabolic activity provided by PET. Starting from our experience, the combined PET/CT evaluation is particularly useful for pulmonary, hepatic, and mammary solid nodules. Whilst the integrated evaluation might not prove helpful just for few types of solid lesions, e.g., renal mass due to the urinary interference[3].

Two factors mainly limit our study. Firstly, the retrospective nature that did not allow a one-time interpretation of the morphological data integrated with the functional ones, as well as to suggest further necessary investigations. Secondly, the lack of follow-up data affected the evaluation of the real impact of IFs detection on patient management and health care costs.

Conclusions

To date, the diagnostic potentialities of hybrid PET/CT imaging remains underestimated, particularly for the morphological portion. The large number of potentially clinically important incidental findings detected in our sample, underlines that co-registered CT images hold precious information often missed. Giving more relevance to co-registered CT with tailored acquisition and reconstruction protocols and dedicated reporting, could further improve the overall diagnostic accuracy of the multimodal imaging. We can speculate that this integrated morphological-metabolic approach could optimize clinical management with impact on time-consuming, healthcare costs and patients' compliance. This subset of cancer patients could represent a model for future application of the full potentialities of the hybrid exam in other oncological settings.

Funding

This research received no external funding.

Statement of Ethics

The present study was performed following the Declaration of Helsinki and approved by the Local Ethics Committee (Prot. n. 828 CE, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Acknowledgments

None.

Conflicts of Interest

The authors declare no conflict of interest.

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