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TITLE: Diagnostic contribution of contrast-enhanced CT as compared to unenhanced low-dose CT in PET/CT staging and treatment response assessment of ^{18}FDG-avid lymphomas: a prospective study

Value of FDG-PET/CECT in avid lymphomas

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ABSTRACT

Objective: The aim of this study was to assess the added diagnostic value of contrast-enhanced CT (CECT) as compared to unenhanced CT (UECT) in PET/CT staging and treatment response assessment of ^{18}FDG-avid lymphomas.

Methods: 170 PET/UECT followed by CECT scans were prospectively performed for staging (n=85) and for treatment response assessment (n=85) of ^{18}FDG-avid lymphomas, during a single session using an integrated 64-slice PET/CT scanner. CECT and UECT images were evaluated separately by two radiologists, whereas PET images by two nuclear physicians. Nodal and extranodal UECT and CECT findings were classified according to the Lugano criteria, and successively compared with PET/CT results, considered the gold standard. In the analysed groups, the agreement rate with the disease status determined via PET was calculated separately for UECT and CECT using Mc Nemar's test on paired data. The added value of the contrast medium was shown by the agreement between the PET and CECT results and the lack of agreement between UECT and PET.

Results: CECT enabled the identification of additional extranodal lesions (hepatic, muscular and gastric) in only 3 staging group cases (3.5%), indicating different stages as compared to UECT, whereas there was absolute agreement between CECT and UECT in terms of treatment response assessment. The added diagnostic value of CECT was lower than the established threshold for clinical relevance (15%). Mc Nemar's test indicated no statistical significance in either group. The incidental findings detected by CECT but not UECT were important for clinical management, but not sufficient to alter lymphoma treatment strategy.

Conclusion: According to our results, it might be possible to exclude CECT examination of ^{18}FDG-avid lymphoma from staging and treatment response assessment, with the consequent advantages of reducing radiation exposure and potential contrast-related risks.

KEYWORDS: PET, CECT, FDG-avid lymphoma, staging, treatment response.

INTRODUCTION

In the Western world, lymphoma represents the fifth most prevalent tumour, with an incidence of 19–20 cases/100,000 inhabitants, with Caucasian males being at greater risk (*1*,*2*).

A major distinction can be made between Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), with the most frequent histotypes being diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and HL (*3*).

In patients with lymphoma, the diagnostic pathway involves multiple radiological and nuclear imaging examinations, and a histotype-dependent follow-up (*4*). Since lymphomas are frequently ^{18}FDG-avid, ^{18}FDG-PET/CT is considered the gold-standard for staging and treatment response assessment (*5*), providing absolutely essential functional and metabolic information regarding lymphomatous lesions, whether morphologically altered or normal (*6*). Moreover, treatment guided by PET/CT staging results in better survival of aggressive NHL compared with therapy based on contrast enhanced CT (*7*). Intravenous iodine contrast media in PET/CT protocols improve identification of anatomic structures, the detection of pathologic lesions and their characterization (*8*). The advantages of contrast is more evident in several anatomical sites where delineation of disease from muscles, vascular structures, or the bowel is critical (*8*).

Lymphoma Staging and Treatment Response Assessment

According to the International Conference on Malignant Lymphoma (2013) (*4*), staging and treatment response assessment of ^{18}FDG-avid lymphomas requires PET/CT examination and a baseline CECT, which should be performed during the same session (*9*). These imaging modalities are also helpful for radiation therapy planning and prognostic evaluation (*10*); further imaging is carried out during therapy for interim evaluation (*11*).

PET/CT includes first the PET scan, then the acquisition of low-dose unenhanced CT (UECT), aimed to correct the attenuation of PET data and to enable anatomical correlation through image fusion. PET-UECT is then followed by the acquisition of a full-dose diagnostic CT with administration of iodinated contrast agent (CECT) (*5*).

PET/CT imaging is interpreted according to the revised Lugano criteria, which combine information about the metabolic activity of the disease furnished by PET with the morphological data from CT (*4*). The Lugano criteria recommend the Ann Arbor classification for staging, while for the purposes of treatment response assessment they recommend the Deauville criteria for PET and the Cheson criteria for CECT (*4*,*5*,*9*).

This routine diagnostic pathway may generate several disadvantages, primarily a high cumulative radiation dose, with the potential risk of radiation-induced carcinogenesis (*12*) over the course of serial CT (staging, interim,

end-of-treatment, follow-up); moreover, the repeated administration of iodinated contrast agents may lead to allergic reactions (*13*), contrast-induced nephropathy (CIN) (*14*) and transient thyroid dysfunction, with potentially dangerous complications such as atrial fibrillation in hyperthyroidism and myxedema coma in hypothyroidism (*15*).

In this context, there have been very few studies on the added diagnostic value that iodine contrast-medium injection may bring to staging or treatment response assessment in FDG-avid lymphomas (*16–22*).

The aim of this study was to evaluate the added diagnostic value of contrast medium injection in staging and treatment response assessment of ^{18}FDG-avid lymphomas, comparing CECT to UECT and considering PET as the gold standard. Indeed, if the added diagnostic value of CECT is not clinically and statistically significant, it may be possible to leave it out of the diagnostic pathway without affecting treatment or outcomes, thereby reducing the potential contrast-related risks and superfluous radiation exposure.

MATERIALS AND METHODS

This study was conducted according to the Declaration of Helsinki; Ethics Committee approval for data collection was obtained (protocol number: 631/2018/Oss/AOUFe) and all subjects signed a written informed consent.

The study prospectively enrolled 170 patients referred to our Onco-haematology Department with a histologically confirmed diagnosis of ^{18}FDG-avid lymphoma over a two-year period (between December 2017 to August 2019). All patients underwent PET/CT followed by CECT, both performed at a single session using an integrated 64-slice PET/CT scanner (SIEMENS MCT BIOGRAPH FLOW MOTION) at our Nuclear Medicine Department in collaboration with the Hospital and University Radiology Unit. The exclusion criteria were: age <18yo, confirmed or suspected pregnancy, breastfeeding, diabetes mellitus, absolute contraindication for iodized contrast medium administration, lymphoma not ^{18}FDG-avid, and immunotherapy. The enrolled patients were assigned to one of two groups: a “Staging” group (ST) for those with a first diagnosis or relapse of lymphoma, and a “Treatment Response” group (TR), in whom the outcome ad interim or at the end of therapy was evaluated in comparison to a baseline examination.

PET/CT protocol

The patients were invited to drink 500mL of water and to rest before the scan, fasting for at least 6 hours, and blood glucose levels were checked before the examination to ensure glycaemia control and to limit bias caused by anomalous uptake of ^{18}FDG. PET acquisition was started 60±5 minutes after intravenous ^{18}FDG injection (an average of 370MBq, with a range of 200–450MBq), with a scan area from skull base to proximal thigh. The patients were scanned with an empty bladder, and in a supine position with their arms raised over their head if possible. First, a low-dose CT was performed (100–120 kV, 30–100 mAs with automatic tube current modulation; rotation tube 0.5 s, pitch 0.8 s and slice thickness 3 mm; reconstruction matrix 512x512 at 3 mm for unenhanced CT and 5 mm for images fused with PET). Subsequently a 3D PET scan was acquired via the FlowMotion technique, requiring a total time of 12–15 minutes with speed 1.10mm/s (range 0.8–1.7 mm/s, depending on body region and administered activity). Syngo.Via Software (Siemens Healthcare, Belgium) was used to fuse and display PET, PET/CT and CT scans with a 3D MIP (max intensity projection) PET view. For semiquantitative analysis, a volume of interest (VOI) was selected, and the contextual standard uptake value (SUV) was calculated.

CECT protocol

After PET/CT scan, a diagnostic CECT of the neck, thorax and abdomen was acquired after a preliminary antero-posterior scout view (100–120 kV, 60–200 mAs with automatic tube current modulation; rotation tube 0.5 s, pitch 0.65 s and slice thickness 2 mm; reconstruction matrix 512x512 and reconstruction thickness 2 mm) and the administration of a dose of intravenous iodinated contrast agent (Omnipaque 350 mg I/ml), modulated according to the weight of the patient, with an average flow of 3 ml/s and bolus-tracking mode. Contrast phases were established by the radiologist according to the clinical scenario, always including a whole-body portal venous phase and, when deemed necessary, also arterial or delayed phases.

Images analysis

Two nuclear physicians evaluated the PET scans independently, blinded to the CECT findings, while two independent radiologists evaluated the CECT and UECT scans, without access to the PET/CT data. The operators were, however, informed of the lymphoma diagnosis. They were asked to assess ST patients on the basis of the revised Ann Arbor/Cotswolds criteria (*4*).

Subsequently, for the TR group scans, the Lugano criteria were applied in blinded manner to each imaging modality, comparing the findings to a baseline acquired via the same imaging technique (corresponding to the staging examination). Higher ^{18}FDG uptakes than background in non-physiological locations were considered consistent with lymphomatous tissue, according to the Deauville criteria. Nodal and extranodal findings in UECT and CECT were separately compared with PET/CT results (gold standard) for each study to assess the agreement between methods.

Statistical analysis

In both ST and TR groups, the agreement rate with the disease status determined via PET was calculated separately for UECT and CECT. Cohen's kappa coefficient was applied to assess the inter-rater reliability. The relative frequencies of agreement between PET and both UECT and CECT were compared using Mc Nemar's test on paired data. The added value of contrast medium was to be considered proven in the case of agreement between PET and CECT findings, but lack of agreement between UECT and PET. Data were analysed using the statistical software Stata version 13 (StataCorp, College Station, TX), and a p-value <0.05 was considered statistically significant.

RESULTS

Study Population

The study comprised 170 PET/CT and CECT scans, of which 85 were assigned to the ST group and 85 to the TR group. In the TR group, of the total of 85 patients, fifty were evaluable for interim treatment response analysis and thirty-five for end-of-treatment assessment. Participants in the study comprised 97 males and 73 females, with a mean age of 53 years (range 20–82), 41 diagnosed with HL and 129 with NHL. A deeper analysis of the population characteristics and histotypes is reported in Table 1.

Staging Group

Agreement with PET was 80% for CECT and 76.5% for UECT ($p<0.001$ in both cases). In 82 out of 85 patients (96.5%), CECT provided the same Ann Arbor stage as assigned by low-dose UECT, and nodal findings were detected equally by CECT and UECT. In only 3 cases (3.5%), CECT identified further extranodal lesions (hepatic, muscular and gastric), assigning a different Ann Arbor stage to low-dose UECT. The first of these patients was affected by HL,

and CECT revealed a paravertebral, intramuscular, nodular, hypodense area, indicating stage IV, while the same area was not visible under UECT, which indicated stage III. On the PET scan, that lesion was hyper-metabolic and therefore indicative of stage IV (Figure 1). The second patient was also affected by HL, and presented several intrahepatic, hypodense, nodular areas on CECT (indicating stage IV) that were not visible on UECT (which indicated stage III). At PET examination, those liver nodules appeared as hypermetabolic foci, indicating stage IV and thus confirming CECT results (Figure 2). In the last patient affected by NHL-DLBCL (diffuse large B-cell lymphoma), CECT revealed heterogeneous thickening of the gastric wall, indicating stage I, which was confirmed by radiotracer uptake in PET images. Conversely, since gastric wall thickening was not evident without iodine contrast media, this patient was classified as without any abnormality on UECT examination (Figure 3). In all the aforementioned cases, PET and CECT staging were concordant, while UECT slightly underestimated the disease stage (Table 2 and Figure 4). As per the main reason for discordance between CT imaging and the gold standard PET, ^{18}FDG uptake showed bone lesions which were not visible under either UECT or CECT.

Our results indicate that the added diagnostic value of CECT is very small, and represented by a 3.5% lack of agreement (95%CI: 0–7.5%) between CECT and UECT staging (Table 3). This value is under the threshold considered clinically relevant (15%), and, furthermore, the Mc Nemar's test showed no statistical significance (p-value=0.083).

Examining the HL (15 cases) and NHL cases (70) separately, the respective agreement of CECT and UECT with PET was 93% and 80% in HL and 77% and 76% in NHL; for both CECT and UECT, the agreement with PET was statistically significant ($p<0.001$). Analysis of the HL and NHL subgroups showed no difference in results (Table 4). In fact, 2 of the 3 cases of discordance between CECT and UECT staging were HL, and the use of contrast medium in these patients would not have modified the treatment strategy. Conversely, in the case of gastric NHL, CECT showing an additional lesion led to a change in treatment. In the HL group, on the other hand, the additional diagnostic value of contrast medium administration (13.3%; CI95%: 0%–30.5%) was just under the threshold considered clinically relevant (15%), although Mc Nemar's test indicated a lack of statistical significance (p=0.157).

Treatment Response

In the 85 patients evaluated according to the Lugano criteria ad interim and at the end of treatment, there was an absolute agreement rate (100%) between CECT and low-dose UECT (32 cases with complete response, 49 with partial response and 4 with stable disease), with both being equally comparable to PET, even in the two different HL

and NHL histotypes (Table 5). Consequently, CECT did not add any contribution to therapy response assessment and may therefore be considered superfluous for the purposes of treatment response assessment. However, as expected, agreement with PET was low for both CECT and UECT (38.8%), but not statistically significant in either case (p=0.104). Bone lesions were the main reason for discordance between PET and UECT/CECT, since they were not visible on CT but were revealed by ^{18}FDG uptake, and the enlarged lymph nodes devoid of ^{18}FDG uptake. Therefore, there is no added value of CECT over UECT in terms of directing lymphoma treatment strategy, regardless of histotype.

Incidental findings

Finally, CECT detected some incidental findings that were not recognizable at UECT alone. These included portal vein thrombosis (Figure 5), pulmonary thromboembolism (Supplemental Figure 1) and spleen infarction (Supplemental Figure 2). None of these influenced lymphomas staging or treatment response assessment, but, for obvious reasons, influenced overall clinical management of the affected patients.

DISCUSSION

This study investigated the additional value of CECT in comparison to UECT for both staging and treatment response assessment purposes in a group of 170 patients with ^{18}FDG-avid lymphoma, considering PET as the gold standard. In the staging group, CECT and UECT displayed 80% and 76.5% agreement with PET, respectively, and agreement was statistically significant in both cases. Lack of agreement was ascribable to the higher sensitivity of PET for some types of lymphomatous bone lesions as compared to UECT and CECT (*17*,*23*). Muscle, liver and gastric lesions, on the other hand, were detected by both PET and CECT, but not recognizable via UECT in the patients assessed for staging. Discriminating between HL and NHL, the agreement with PET was always significantly greater than 75% for both CECT and UECT.

Upon closer analysis of the three cases (3.5%) of lack of agreement between CECT and UECT in the ST group, in the two HL patients the correct staging provided by CECT would not have changed the treatment strategy, while in the third case (i.e.NHL) the correct CECT staging led to a change in clinical management with respect to what would have been prescribed on the basis of UECT findings alone. In light of this, in the HL subgroup, the added diagnostic

value of CECT for staging purposes was of 13.5%, close to the clinically relevant threshold (15%), but this value was influenced by the limited number of patients (n=15); while in the larger subgroup of NHL (n=70), this value was clearly lower than the threshold (1.4%). Therefore, a potential increased diagnostic value of CECT in HL compared to NHL should be demonstrated in a larger sample group.

On the basis of our findings, however, PET/UECT staging of ^{18}FDG-avid lymphomas should be suggested as the imaging modality of choice. This conclusion is in line with that by Van Hamersvelt and colleagues, who recommended ^{18}FDG-PET/UECT as the primary imaging modality for staging ^{18}FDG-avid lymphomas following a similar study, comparing the staging findings of ^{18}FDG-PET/UECT and CECT in a group of 29 patients newly diagnosed with ^{18}FDG-avid lymphoma (*16*). In that study, CECT indicated a different stage to UECT on the basis of Ann Arbor classification in 7% of patients, however without changes in therapeutic approach, thus supporting the hypothesis that iodinated contrast media is unnecessary for staging purposes.

Indeed, another prospective study by Rodriguez-Vigil et al. found no difference between unenhanced low-dose ^{18}FDG-PET/CT and contrast-enhanced full-dose ^{18}FDG-PET/CT in 47 patients newly diagnosed with lymphoma, except that the latter technique showed less indeterminate findings and a higher number of extranodal lesions (*24*). UECT and CECT displayed good correlation in terms of nodal and extranodal lesion detection, and the authors therefore concluded that unenhanced low-dose PET/CT could be used for initial imaging in lymphomas, reserving CECT for only selected cases. However, similarly to our results, they found that contrast-enhanced full-dose ^{18}FDG-PET/CT detected important incidental findings in 2 patients (4.3%), that were not observed via unenhanced low-dose ^{18}FDG-PET/CT (*24*).

In this regard, another study by Pinilla et al. found comparable results regarding nodal involvement and parenchymal evaluation, bone marrow included. In unenhanced low-dose and contrast-enhanced full-dose ^{18}FDG-PET/CT obtained in 101 patients with newly diagnosed lymphoma, the authors showed that contrast-enhanced PET/CT revealed important incidental findings in 6 patients (5.9%). They also concluded that there are no significant differences between unenhanced low-dose ^{18}FDG-PET/CT and contrast-enhanced full-dose ^{18}FDG-PET/CT in terms of initial lymphoma staging accuracy, but that CECT enables the detection of incidental findings not revealed using UECT (*25*).

However, Sabaté-Llobera et al., who assessed 28 patients affected by DLBCL assessed for staging purposes via ^{18}FDG-PET/UECT and CECT, found disagreement between the two techniques in 21% of cases, in half of which

treatment strategy would have been impacted. In particular, they concluded that PET/UECT is more sensitive than CECT in detecting nodal and extranodal lesions, and therefore suggested that contrast media administration might be avoidable (*19*). Alnouby et al., analysing a group of 144 patients with various lymphoma histotypes including those weakly avid for ^{18}FDG, also reported results indicating that PET/UECT assessment is more sensitive for extranodal involvement than CECT (respective sensitivity of 97% and 89.6%, and accuracy of 91.7% and 87.5%), especially in the spleen, bone and bone marrow, since ^{18}FDG highlights metabolically active areas in structures of normal morphology (*23*). Similarly, Panebianco et al., in their study of 62 cases of newly diagnosed HL, found that CECT was less sensitive than ^{18}FDG-PET/CT in the detection of some bone marrow lesions, but more reliable in assessing liver tumours, while no difference emerged between the two imaging modalities in terms of detecting lung involvement; they confirmed that PET/CT allows better staging in HL through the detection of nodal lesions (*17*). Furthermore, in a recent study, Paone et al. investigated the advantage of the use of contrast in terms of detecting sites of disease in 30 patients with FL in end-of-treatment low-dose PET/CT (agreement rate 87%), and concluded that the clinical impact of CECT is limited to cases with suspected residual disease in mesenteric and iliac nodal stations (*18*).

Similarly, in our study the additional diagnostic value of contrast material in staging and treatment response assessment in ^{18}FDG-avid lymphomas was limited to very few cases, in which CECT would have assigned a less advanced Ann Arbor stage than the gold standard low-dose ^{18}FDG-PET/CT, and in only one case would it have affected the treatment pathway. Since the added diagnostic value of 3.5% we found for CECT is not statistically significant, this would suggest that it may be possible to omit CECT from the process of staging ^{18}FDG-avid lymphomas, irrespective of their histotype. Nonetheless, should our results be confirmed in a larger sample, CECT could still have a role in HL staging, because the added value of contrast was close to the threshold of clinical significance.

In assessing treatment response, on the other hand, CECT did not demonstrate any advantage over UECT in ^{18}FDG-avid lymphomas, confirming that UECT should be the first-choice low-dose ^{18}FDG-PET/CT imaging mode in this type of disease. The main additional information provided by contrast enhancement was the detection of extranodal involvement, which was, however, always revealed by the gold standard PET. Although CECT allowed the detection of additional incidental findings unrelated to the lymphoma, these were clinically significant in only a few cases and did not affect lymphoma staging or treatment response assessment. Consequently, these findings did not increase the diagnostic value of CECT in the assessment of ^{18}FDG-avid lymphomas, with the addition of a

consistent increase of radiation exposure (*26*). An advantage of our study is the use of a standardized protocol in which CECT was performed after PET/CT, preventing inaccuracies in SUV quantification due to the artifacts of iodine contrast attenuation (*26*). Both the exams were executed in a single time session, allowing a better overlapping of scan images acquired. Some limitations of the study should be also acknowledged. First, it is single-center study. Second, the study protocol did not include the collection of estimates of the effective dose delivered by PET / CT and CECT for each acquisition. Finally, the different number of patients in the HL and NHL subgroups makes the diagnostic added value of CECT difficult to compare based on the different histotypes: in particular, in the HL population, it should be calculated on a more representative sample size to confirm our data.

CONCLUSION

According to our data, it is conceivable that, in the ^{18}FDG avid lymphoma examination, CECT should be justifiable only in patients with negative PET examination and equivocal UECT findings, and in patients with positive PET lesions suspicious of being non-lymphomatous lesions.

Since the most important benefit of contrast-enhanced CT data as part of the combined PET/CT examination relates to more precise anatomic localization of disease, by differentiation of the lesion from its surrounding structures, CECT might be useful for planning radiotherapy, interventional procedures, and surgery.

Limiting the field of application of CECT to the aforementioned cases could prevent the undue exposure of patients, both young and elderly, to the drawbacks linked to repeated irradiation, and those ascribable to iodinated contrast medium. Furthermore, this approach could also lessen the financial burden, allowing better management and more efficient distribution of resources. However, further studies are required to confirm these results in a larger cohort, in order to better select those patients who really need CECT examination, especially in cases of suspected extranodal disease.

KEY-POINTS

Question: Does contrast-enhanced CT (CECT) have an added value over unenhanced CT (UECT) in PET / CT staging and assessment of response to treatment of ^{18}FDG avid lymphomas?

Pertinent findings: In this prospective study, 85 patients underwent PET/UECT followed by CECT scans for staging and 85 patients for treatment response assessment of ^{18}FDG-avid lymphomas. Only in 3.5% of patients, CECT allowed a different staging than UECT, while there was an absolute agreement between CECT and UECT in the assessment of treatment response.

Implications for patient care: CECT examination in PET / CT staging and treatment response assessment of FDG avid lymphoma may be useless.

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Figure Legends:

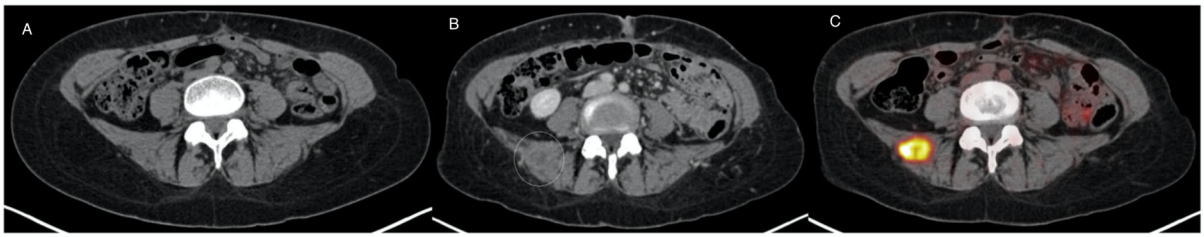


Figure 1. In a patient with Hodgkin lymphoma, UECT did not detect the lesion in the right paravertebral muscles (A) revealed as a hypovascular nodular area (circle) by CECT (B), thereby indicating Ann Arbor stage III instead of stage IV suggested by CECT; the corresponding hyper-metabolic lesion evident on FDG-PET (C).

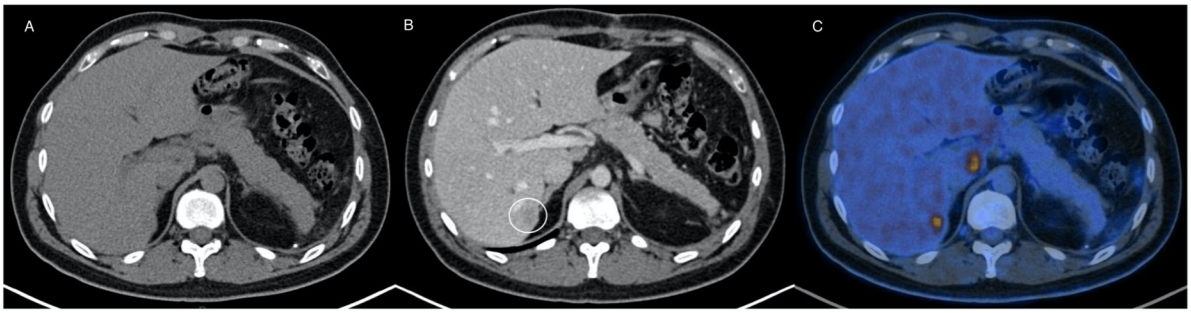


Figure 2. In a patient with Hodgkin lymphoma, UECT did not detect the hepatic lesion in the right lobe (A), revealed as a hypodense nodular area (circle) by CECT (B), thereby indicating Ann Arbor stage III instead of the stage IV suggested by CECT and the hyper-metabolic focus displayed under FDG-PET (C).

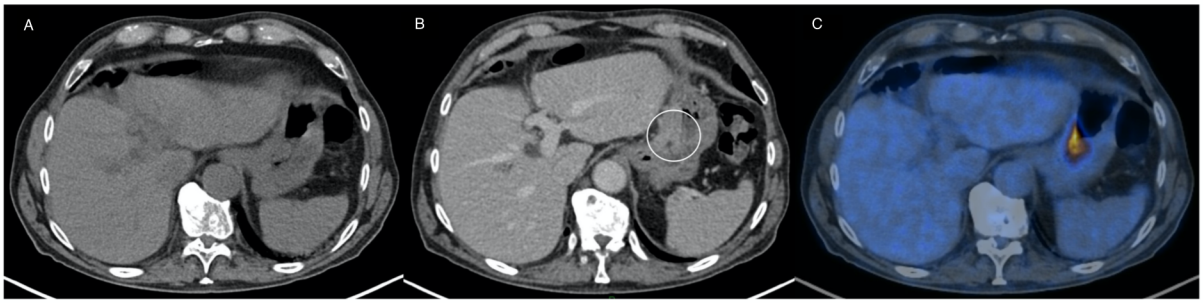
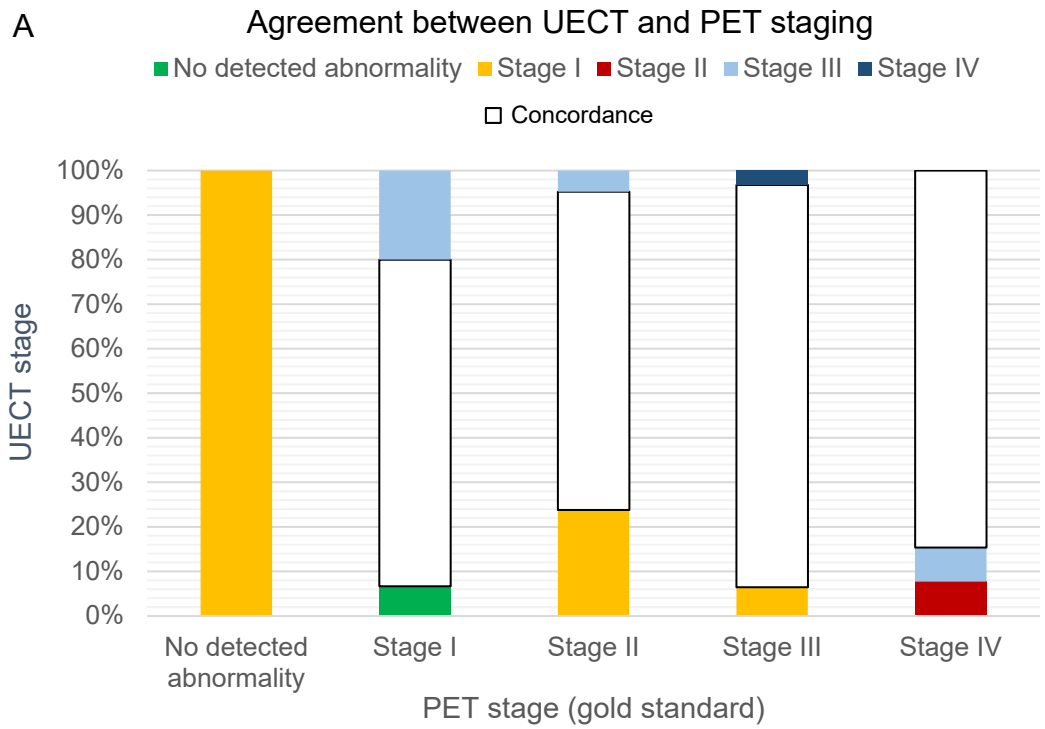


Figure 3. In a patient with non-Hodgkin lymphoma, UECT did not show the gastric lesion (A), depicted as a thickened gastric wall (circle) by CECT (B), staging him as a patient with no detected abnormality instead of the stage I indicated by CECT and the area of FDG-uptake shown by PET (C).



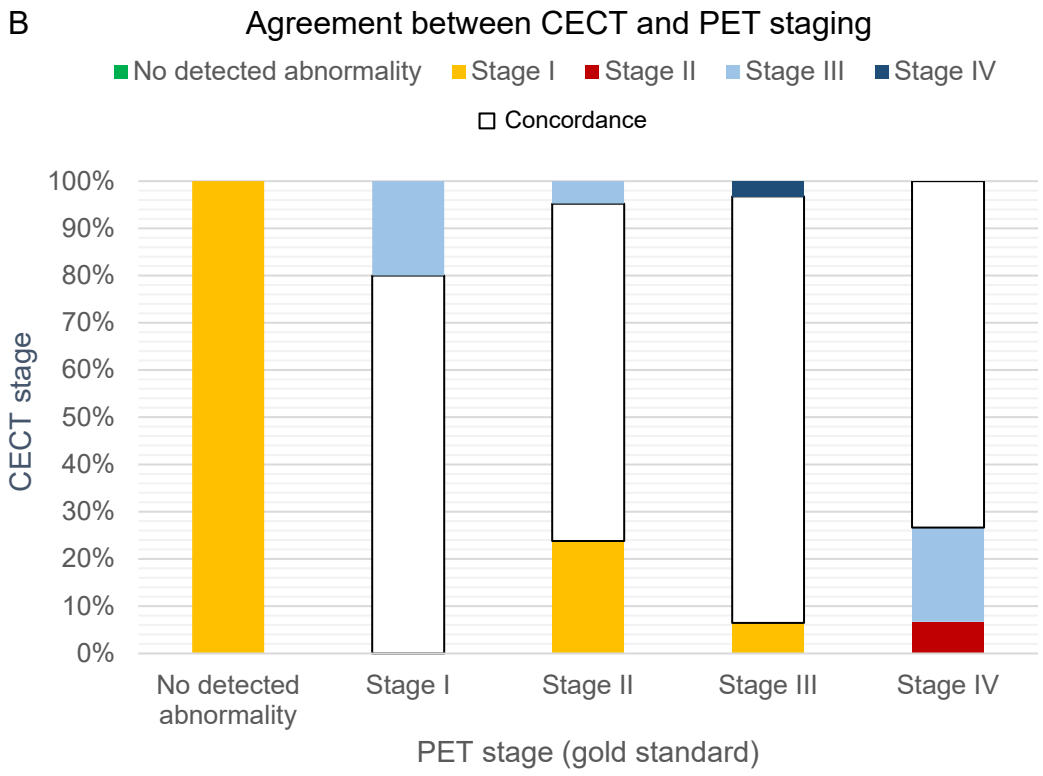


Figure 4. White boxes in the bar charts represent the agreement between Ann Arbor stages assigned on the basis of PET as compared to the two CT techniques, respectively UECT (A) and CECT (B).

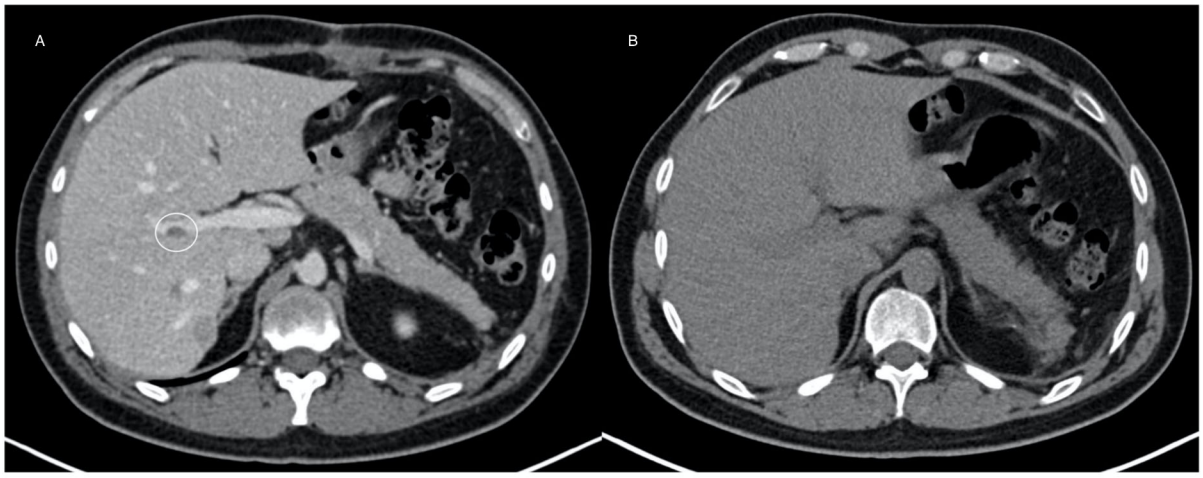
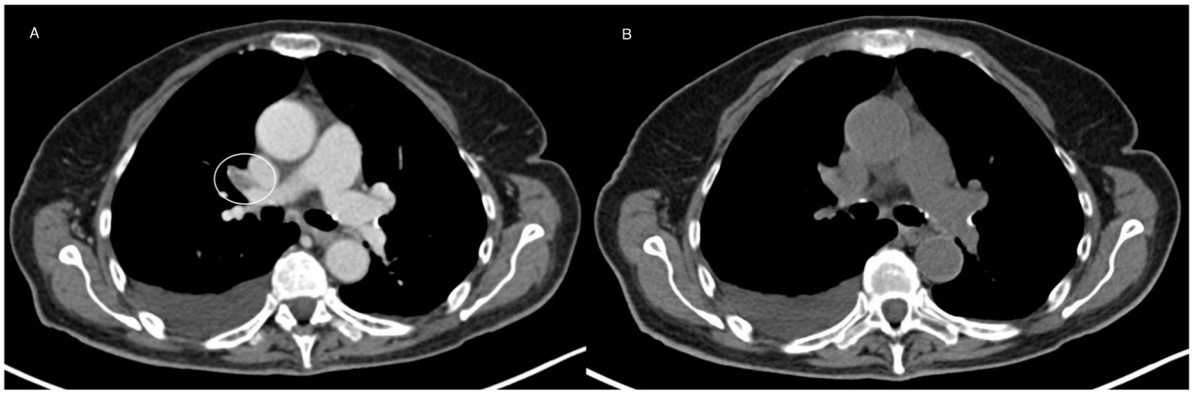
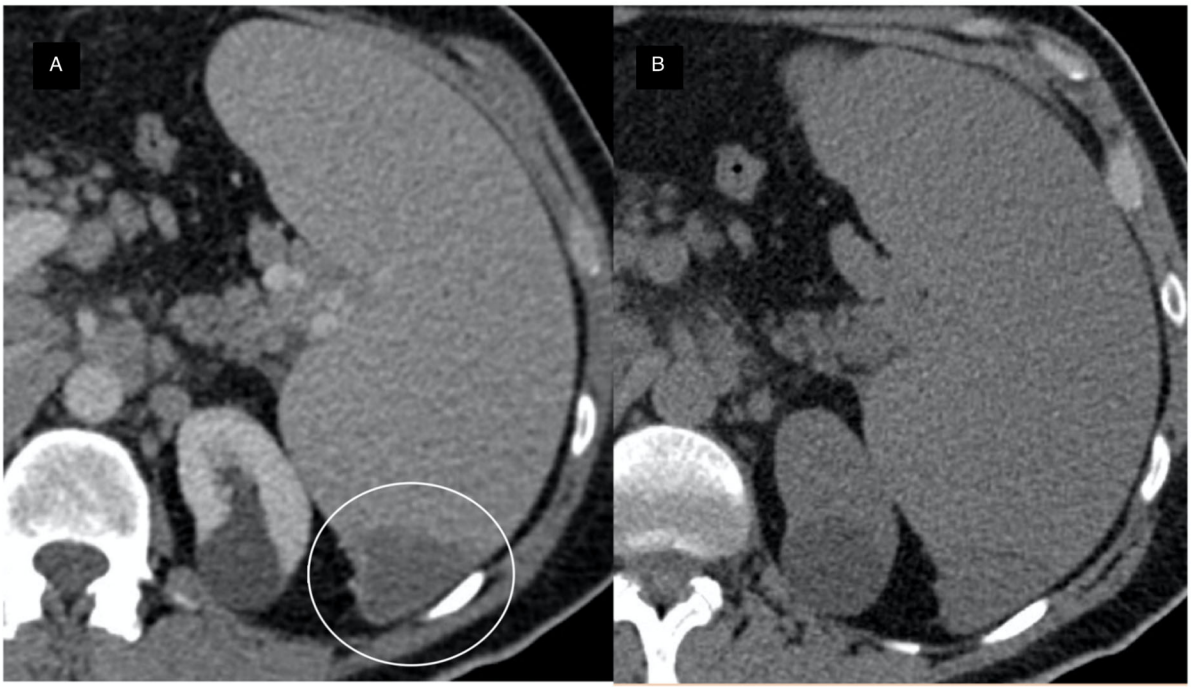


Figure 5. A patient with non-Hodgkin lymphoma presenting with portal vein thrombosis (circle) detected by venous-phase CECT (A) but not recognizable on UECT (B).



Supplemental Figure 1. A patient with non-Hodgkin lymphoma with thromboembolism of the right pulmonary artery (circle) detected by venous-phase CECT (A) but not recognizable on UECT (B).



Supplemental Figure 2. Patient with non-Hodgkin lymphoma with splenic infarction visible on venous-phase CECT (A) but not fully recognizable at UECT (B).

	Staging group characteristics N (%) n = 85	Treatment response group characteristics N (%) n = 85
Age (years)		
Average (range)	57.6 (24–82)	48.2 (20–81)
Sex		
Male	50 (59%)	47 (55%)
Female	35 (41%)	38 (45%)
Hodgkin's lymphoma	15 (18%)	26 (31%)
Non-Hodgkin's lymphoma	70 (82%)	59 (69%)
DLBCL	30 (35%)	28 (33%)
Follicular	17 (20%)	9 (11%)
Mantle cells	8 (9%)	7 (8%)
Marginal zone	2 (2%)	5 (6%)
Burkitt's Lymphoma	2 (2%)	7 (8%)
Others*	11 (13%)	3 (3%)
Performance status (ECOG)		
0	73 (86%)	79 (93%)
1	8 (10%)	4 (5%)
2	2 (2%)	1 (1%)
Missing	2 (2%)	1 (1%)
IPI		
0	10 (12%)	5 (6%)
1	8 (9%)	8 (9%)
2	9 (11%)	9 (11%)
3	7 (8%)	13 (15%)
4	1 (1%)	4 (5%)
Missing	50 (59%)	46 (54%)
LDH		
Less than or equal to ULN	53 (63%)	54 (64%)
Greater than ULN	25 (29%)	29 (34%)

Missing	7 (8%)	2 (2%)
Bulky mass	13 (15%)	7 (8%)

∗Peripheral T-cell lymphoma, gastric lymphoma, nasal NK/T-cell lymphoma, anaplastic large cell lymphoma, indolent B-cell lymphomas, angioimmunoblastic lymphoma, high-grade B-cell lymphoma, non-specific high-grade lymphoma

ULN = Upper limit of normal

Table 1. Staging group and Treatment Response group characteristics.

		PET					
	Stage	**-**	**I**	**II**	**III**	**IV**	**Total**
UECT	**-**	**0**	1	0	0	0	1
	I	1	**11**	5	2	0	19
	II	0	0	**15**	0	1	16
	III	0	3	1	**28**	5	37
	IV	0	0	0	1	**11**	12
	Total	1	15	21	31	17	85

		PET					
	Stage	**-**	**I**	**II**	**III**	**IV**	**Total**
CECT	**-**	**0**	0	0	0	0	0
	I	1	**12**	5	2	0	20
	II	0	0	**15**	0	1	16
	III	0	3	1	**28**	3	35
	IV	0	0	0	1	**13**	14
	Total	1	15	21	31	17	85

Table 2. Agreement of UECT (upper table) and CECT (lower table) stages with PET staging according to Ann Arbor Classification, with cases of agreement highlighted in bold type. In 65 of 85 cases, the UECT agreed with PET (76.5% agreement; 95%CI: 66.0%–85.0%; p-value <0.001 and k=0.676). In 20 of 85 cases the UECT disagreed with PET: in 6 patients (7%) UECT over-staged and in 14 patients (16.5%) it under-staged. These data are plotted in Figure 4A. In 68 of 85 cases the CECT agreed with PET (80% agreement; 95%CI: 69.9%–87.9%; p-value <0.001 and k=0.726). In 17 of 85 cases the CECT disagreed with PET: in 6 patients (7%) CECT over-staged and in 11 patients (13%) it under-staged. These data are plotted in Figure 4B.

- *no abnormality detected*

		UECT					
	Stage	**-**	**I**	**II**	**III**	**IV**	**Total**
CECT	**-**	**0**	0	0	0	0	0
	I	1	**19**	0	0	0	20
	II	0	0	**16**	0	0	16
	III	0	0	0	**35**	0	35
	IV	0	0	0	2	**12**	14
	Total	1	19	16	37	12	85

Table 3. Agreement between CECT and UECT staging according to Ann Arbor Classification, with cases of agreement highlighted in bold type.

- *no abnormality detected*

		PET					
	NHL Stage	**0**	**I**	**II**	**III**	**IV**	**Total**
UECT	**NAD**	**0**	1	0	0	0	1
	I	1	**9**	5	2	0	17
	II	0	0	**10**	0	1	11
	III	0	3	1	**25**	2	31
	IV	0	0	0	1	**9**	10
	Total	1	13	16	28	12	70

		PET					
	HL Stage	**0**	**I**	**II**	**III**	**IV**	**Total**
UECT	**NAD**	**0**	0	0	0	0	0
	I	0	**2**	0	0	0	2
	II	0	0	**5**	0	0	5
	III	0	0	0	**3**	3	6
	IV	0	0	0	0	**2**	2
	Total	0	2	5	3	5	15

		PET					
	NHL Stage	**0**	**I**	**II**	**III**	**IV**	**Total**
CECT	**NAD**	**0**	0	0	0	0	0
	I	1	**10**	5	2	0	18
	II	0	0	**10**	0	1	11
	III	0	3	1	**25**	2	31
	IV	0	0	0	1	**9**	10
	Total	1	13	16	28	12	70

		PET					
	HL Stage	**0**	**I**	**II**	**III**	**IV**	**Total**
CECT	**NAD**	**0**	0	0	0	0	0
	I	0	**2**	0	0	0	2
	II	0	0	**5**	0	0	5
	III	0	0	0	**3**	1	4
	IV	0	0	0	0	**4**	4
	Total	0	2	5	3	5	15

Table 4. Ann-Arbor staging agreement with PET for UECT (upper tables) and CECT (lower tables) in non-Hodgkin's and Hodgkin's Lymphoma. The cases of agreement are highlighted in bold type. The over-staging of 4 NHL patients on CECT and UECT compared to PET, with consequent therapeutic planning change, is due to enlarged nodes (longest diameter in axial plane > 1.5 cm) localized in both sides of the diaphragm without significant PET uptake.
- *no abnormality detected*

	PET				
TR Response Classes	**CR**	**PR**	**SD**	**PD**	**Total**
UECT/CECT	**CR**	**31**	0	0	1	32
	PR	44	**2**	1	2	49
	SD	4	0	**0**	0	4
	PD	0	0	0	**0**	0
	Total	79	2	1	3	85

||	PET				
TR - HL Response Classes	**CR**	**PR**	**SD**	**PD**	**Total**
UECT/CECT	**CR**	**22**	0	0	1	23
	PR	32	**1**	1	0	34
	SD	2	0	**0**	0	2
	PD	0	0	0	**0**	0
	Total	56	1	1	1	59

III	PET				
	TR - NHL Response Classes	**CR**	**PR**	**SD**	**PD**	**Total**
UECT/CECT	**CR**	**9**	12	2	0	23
	PR	0	**1**	0	0	1
	SD	0	0	**0**	0	0
	PD	0	2	0	**0**	2
	Total	9	15	2	0	26

Table 5. Agreement between UECT/CECT and PET response classes according to Lugano criteria in the TR group(I), also divided into HL(II) and NHL(III). The cases of agreement are highlighted in bold type. In 33 of 85 cases, UECT and CECT agreed with PET (38.8% agreement; 95%CI: 28.4 %–50.0%), a value that is not statistically significant (p-value=0.104 and k=0.038).