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Research paper

Comparison of ^{18}F FDG PET-CT AND CECT in pretreatment staging of adults with Hodgkin's lymphoma

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ABSTRACT

We compared 2-[fluorine-18] fluoro-2-deoxy-D-glucose PET-CT and contrast-enhanced computed tomography (CECT) in 62 consecutive patients with newly diagnosed Hodgkin Lymphoma (HL), aiming to provide evidences that may spare CECT from the staging procedures of HL patients.

Among a total of 1448 nodal sites examined, disease involvement was detected in 232 (16%) and 280 (19.3%) nodal areas by CECT and PET-CT, respectively ($P < 0.01$). Sensitivity of CECT in detecting disease involvement ranged from 0% for internal mammary region (7 cases) and Waldayer's ring (1 case) to 100% for mediastinum.

A total of 248 extranodal areas were examined. CECT and PET-CT identified disease involvement in 19 (7.7%) and 25 (10.1%) extranodal areas, respectively (P = n.s). Compared to PET-CT, CECT detected a lower number of cases with bone and/or bone marrow involvement ($P = 0.05$), whereas no differences were detected at the level of lung. By contrast, CECT identified liver lesions in four patients versus three identified by PET-CT.

In comparison to CECT, PET-CT upstaged 6 patients (9.7%) and downstaged 1 patient (1.6%).

We showed that PET-CT modified treatment strategy in five (8.1%) cases not only as a result of stage advancement (2 cases) but also of a different prognostic stratification in patients with localized disease (3 cases), due to the better sensitivity in detecting nodal involvement.

In conclusion, our data, confirm the superiority of PET-CT in detecting disease involvement at diagnosis of HL, and further supports the possibility to replace CECT with PET-CT in the initial staging of HL.

1. Introduction

Hodgkin Lymphoma (HL) is a chemo-radiosensitive cancer with a five-year survival rate over 85% with current therapies [1]. However, there are serious long-term therapy related adverse events such as second cancers, cardiac and peripheral vascular disease, pulmonary disease, infertility, sexual dysfunction, etc. Therefore, it is extremely important to reduce the long-term side effects, reducing the amount and toxicity of poly-chemotherapies and improving staging procedures [2,3].

According to the Lugano criteria, Chest X-ray and a total body contrast-enhanced computed tomography (CECT) are mandatory staging tools. In addition, according to this criteria the baseline 2-[fluorine-18] fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography (PET-CT) is still only recommended for routine staging of FDG-avid nodal lymphomas such as HL, despite its high specificity and sensitivity for staging and response assessment in lymphoma [4]. Very recently, due to the relevance gained by PET-CT in the evaluation of the early response to treatment, the IWG criteria recommended that PET-CT should be added to CECT in the staging of FDG-avid lymphomas to provide a baseline against which response is more accurately assessed [5].

However, the possibility of avoiding CECT has not been firmly established because of the data available to date are inconclusive. In fact, some are derived from old studies in which PET was not combined with CT imaging [6–13], and others included small series of HL patients

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[14–20]. Nevertheless, several studies seem to question the central role of CECT for initial staging of HL. Recent reports showed that PET-CT had a significant influence in defining the stage of HL, with upstaging of 14%–28% and down staging of 6% of patients, leading to a change of the treatment strategy in around 6–16% of cases [21–23].

Herein we compared these two imaging methodologies in the pre-treatment staging of HL patients aiming to evaluate the possibility to replace CECT with PET-CT in the evaluation of initial extent of disease.

2. Patients and methods

2.1. Patients

62 consecutive patients (33 men and 29 women [ratio, 1.14]) with histological diagnosis of HL between January 2010 and March 2017 at St. Maria Goretti's Hospital in Latina., previously untreated and for whom it was possible to recover PET-CT and CECT images, were retrospectively evaluated.

Mean age was 36 yr. ± 16.4 [standard deviation]). The classical histological variants of HL were diagnosed in 59 patients: Nodular Sclerosis in 38, Mixed Cellularity in 10, Lymphocyte-rich in 5, Lymphocyte-depleted in 1, Hodgkin disease not specified in 5. The remaining 3 patients had a Nodular Lymphocyte-Predominant Hodgkin Lymphoma. B symptoms were reported by 22 patients.

The extent of disease was evaluated by pre-treatment PET-CT and CECT scan of neck, chest, abdomen and pelvis, in line with ESMO Clinical Practice Guidelines [24].

The median interval between CECT and PET-CT scans was 10 days, whereas on average it was of 14.29 days. In accordance with results reported by Ujjani et al. [25], since August 2016 we have omitted unilateral bone marrow biopsy (BMB) at initial evaluation: thus, histological assessment of bone marrow involvement was performed in 53 out of 62 patients.

Prognostic stratification of patients, for limited and advanced stages, was carried out according to EORTC criteria [26] and to the International Prognostic System (IPS) defined by Hasenclever et al [27].

2.2. PET-CT and CECT scanning

All patients underwent baseline PET-CT according to standard procedures [28]. Patients had been fasting for at least 6 h and, before tracer delivery, had blood glucose levels lower than 160 mg/dl. PET scans (GE Discovery ST, Milwaukee, USA), from the base of the skull to the mid-thigh, were registered 60 min after intravenous administration of 37 MBq/Kg 2-[fluorine-18] fluoro-2-deoxy-D-glucose (^{18}F FDG) tracer, according to the body mass index of the patient. A multilayer low-dose unenhanced CT (16-layer tube) of the neck, chest and abdomen was performed in order to obtain attenuation correction of PET and structural correlate to optimize PET image evaluation. Standardized uptake values (SUVs) were also reported. Biological volume of bulky disease was also assessed using segmentation threshold of 42% of SUV max in order to eliminate partial volume effect through dedicated software.

All patients performed pre-treatment CECT according to standard procedure. Each patient was imaged using a 128-row multi-detector CT system (Lightspeed VCT, GE Healthcare, Milwaukee, WI) in head-first supine position. Unenhanced and enhanced CT scans were included. Iodinated intravenous contrast medium dose was 1.35–1.5 ml/Kg BW. CT images were registered 60 s after tracer bolus delivery. Total body scans, inclusive of neck, chest, abdomen, and pelvis, comprehensive of all lymphatic localizations were acquired. Slice thickness was 1 mm.

2.3. Image analysis

Two experienced specialists, a radiologist and a nuclear medicine physician, retrospectively evaluated pre-treatment CECT and PET-CT images of 62 patients. The experts were not aware of the original stage of patients. After the review of images, each single case was discussed and evaluated by a team composed of the nuclear medicine physician, radiologist and hematologist. The discrepancies were discussed until a consensus.

Ann Arbor system (modified according to Cotswolds system) was used in order to determinate the extent of the disease [29]. The nodal and extranodal sites involvement was defined in accordance with Lugano criteria. In particular, lymph nodes greater than 15 mm in longest diameter (LDi) and extranodal lesion with LDi greater than 1.0 cm were considered pathological at CECT scan. Bulky disease, defined as a single nodal mass ≥10 cm at any level of thoracic vertebrae at CECT, was measured both in CECT and in PET-CT images with the aim of comparing these two methods and demonstrating that PET-CT, if adopted as the only technique in the staging of HL, could replace CECT also in the assessment of Bulky disease. At PET-CT, nodal sites with increased ^{18}F FDG uptake were considered involved by HL, spleen involvement was defined by the presence of diffuse, solitary mass, miliary lesions or nodules of ^{18}F FDG uptake, whereas diffuse ^{18}F FDG uptake and mass characterized liver involvement [4].

In this study, for each patient, 24 lymph node areas were evaluated: Waldeyer's ring, cervical, infraclavicular, internal mammary, axillary and pectoral, mediastinal, hilar, epitrochlear and brachial, spleen, mesenteric, paraaortic, iliac, inguinal and femoral, and popliteal. We also defined 4 extranodal sites of interest: lungs and pleura, bones, bone marrow (BM), and liver. Therefore, for 62 patients, 1488 lymph node areas and 248 extranodal sites were exanimated.

Three groups of patients were identified: patients with concordant stage and sites involvement, patients with concordant stage but different sites involvement, and patients with discordant stage at CECT and PET-CT scan.

Furthermore, in cases of discrepancy, post-treatment PET-CT and CECT images were reviewed. At initial staging any equivocal area identified by CECT scans, but not by PET-CT images, was considered as true positive in presence of a post-treatment metabolic complete response (PET Deauville Score ≤3); conversely, in the presence of a persistent positivity at the post-treatment PET analysis (PET Deauville Score > 3), the discrepancy was been solved by histological examine.

2.4. Statistical analysis

Data are shown as mean ± standard deviation for numerical and frequency (percent) for qualitative variables. Negative sites with both CECT and PET-CT were regarded as true negative. The discrepancies that emerged from the two techniques were considered on the basis of the revision of the post-treatment images. Fisher's exact test was used to evaluate statistical correlation between lesions assessed by PET-CT and CECT in each site. A statistically significant association was defined as P value of less than 0.05.

3. Results

Based on the results of the review of PET-CT and CECT scans, concordant results in terms of stage definition and number of site involvements were detected in 36 (58.1%) patients. Nineteen (30.6%) cases differed for the number of sites involved and 7 (11.3%) cases showed discordant stage.

Table 1 lists the results in terms of true positive/negative, false negative and sensitivity of the two imaging techniques grouped according to the different nodal and extranodal areas considered. Among a total number of 1448 nodal sites examined, CECT and PET-CT detected disease involvement in 232 (16%) and 280 (19.3%) nodal areas, respectively ($P < 0.01$). Compared to PET-CT, sensitivity of CECT in detecting nodal disease involvement ranged from 0% of internal mammary region (7 cases) and of Waldayer's ring (1 case) to 100% of the mediastinum. With regard to extranodal sites, a total number of 248

Table 1
Imaging results of regional analysis conducted by FDG PET-CT and CECT.

Site	18 F FDG PET-CT				CECT			
	TP (PET + sites)	TN (PET – sites)	FN (PET- and CECT + sites)	Sensitivity	TP (CECT + sites)	TN (CECT – sites)	FN (PET + and CECT– sites)	Sensitivity
Cervical left	46	16	0	100%	43	16	3	93%
Cervical right	39	23	0	100%	32	23	7	82%
Right Waldayer's ring	1	61	0	100%	0	61	1	0%
Axillary left	12	50	0	100%	8	50	4	67%
Axillary right	13	49	0	100%	10	49	3	77%
Sternal	1	61	0	100%	0	61	1	0%
Hilar left	16	46	0	100%	14	46	2	88%
Hilar right	19	43	0	100%	18	43	1	95%
Mediastinal	48	14	0	100%	48	14	0	100%
Right internal mammary	3	59	0	100%	0	59	3	0%
Left internal mammary	4	58	0	100%	0	58	4	0%
Paraaortic	16	46	0	100%	15	46	1	94%
Mesenteric	11	51	0	100%	6	51	5	55%
Iliac left	8	54	0	100%	6	54	2	75%
Iliac right	12	50	0	100%	9	50	3	75%
Inguinal ad femoral left	8	54	0	100%	6	54	2	75%
Inguinal ad femoral right	6	56	0	100%	5	56	1	83%
Spleen	17	45	0	100%	12	45	5	71%
Subtotal lymph node	280	836	0	100%	232	836	48	83%
Lung and pleura	7	55	0	100%	7	55	0	100%
Liver	3	58	1	75%	4	58	0	100%
Bon and bone marrow	15	47	0	100%	8	47	7	53%
Subtotal extranodal	25	160	1	96%	19	160	7	73%
TOTAL	305	996	1	100%	251	996	55	82%

TP: true positive; TN: true negative; FP: false positive; FN: false negative.

Table 2
Comparison of CT stage and PET stage.

CT / PET	I	II	III	IV	PET Stage
I	6				6
II	1	27			28
III		3	10	1	14
IV			2	12	14
CT Stage	7	30	12	13	Total: 62

Legend: Concordant stage □ Upstaged PET cases Upstaged CT cases.

areas were examined, CECT and PET-CT identified a disease involvement in 19 (7.7%) and 25 (10.1%) extranodal areas respectively (P = n.s). Compared to PET-CT, CECT detected a lower number of cases with bone and/or bone marrow involvement (P = 0.05), whereas no differences were detected at the level of lung. By contrast, CECT identified liver lesions in four patients versus three identified by PET-CT.

These observations led to different patients' stage stratification. As illustrated in Table 2, according to CECT examination, 7 patients presented with stage I, 30 with stage II, 12 with stage III, and 13 with stage IV, whereas PET-CT scan identified 6 patients with stage I, 28 with stage II, 14 with stage III, and 14 with stage IV. Therefore, CECT and PET-CT were discordant for stage allocation in 7 out of the 62 H L patients (11.3%). Of these, PET-CT upstaged 6 cases (9.7%) and downstaged the remaining case (1.6%). The stage advancement due to PET-CT were stage I to II in one case, stage II to III in three patients and stage III to IV in two patients. By contrast, the results of CECT allowed a stage progression in only one case, from stage III to IV.

In this last case, CECT, contrary to PET-CT, identified a liver lesion. The review of the end-of-treatment CECT images showed a complete regression of the liver lesion, in accordance with the metabolic complete response at PET-CT, confirming the liver localization of HL at staging. Among the 29 H L patients with a localized I—II A stage, CECT allocated 20 patients in the favorable group and 9 in the unfavorable one; conversely PET-CT identified 17 and 12 patients as favorable and unfavorable, respectively.

Therefore, as reported in Table 3, compared to CECT, PET-CT scans resulted in a change of treatment strategy in 5 of the 62 patients (9.7%). Of these, three early stage HL that were reclassified as unfavorable by PET-CT, and two cases because of progression from a localized to an advanced stage (IIA versus III stage).

3.1. Bulky disease

In Table 4 we report the evaluation of bulky nodal areas assessed by CT without contrast enhancement, performed in co-registration with all ^{18}F FDG PET images, and CECT. As shown, the observed differences were not significant, ranging from – 0.3 to + 0.6 cm. In addition, PET-CT confirms all the bulky disease evidenced by CECT.

By contrast, PET-CT, failed to detect the endovascular thrombosis in one of the patients with bulky disease.

Table 3
Causes of change of treatment strategy according to PET-CT analysis.

Patient	Age	CT Stage	Reason for change of treatment	Site of discrepancy identified by PET-CT	End treatment PET Response
1	16	IIA	PET stage advancement (IIIsA)	Spleen	CR
2	22		PET stage advancement (IIIA)	Paraaortic	CR
3*	34	IIA	Progression to unfavourable prognosis	3 nodal areas + Cervical right	CR
4*	24			3 nodal areas + Hilar right	CR
5*	28			3 nodal areas + Left internal mammary	CR

CR: Complete response.
* patients with a change in prognosis due to the presence of ≥ 4 nodal stations involved (EORTC criteria).

Table 4
FDG PET-CT and CECT in evaluation of bulky disease.

Patients	1	2	3	4	5
CECT Bulky size (longest Diameter/cm)	16	10.8	13.1	10	14
FDG PET-CT Bulky size (longest Diameter/cm)	15.7	11.4	13.3	10.2	13.6

4. Discussion

The present study, although retrospective and carried out in a small series of 62 H L patients, confirms the value of PET-CT in identifying HL localizations both in nodal and in extranodal areas, and due to the superior sensitivity of this technique with respect to CECT, suggests that PET-CT should replace CECT in the initial staging of patients with HL.

These findings are similar to those initially reported by Rigacci et al, in a study in which ^{18}F FDG PET was prospectively compared to CECT in 186 H L patients, showing that ^{18}F FDG PET led to an upstage in 14% and to a downstage in only 1% of patients, with a change of treatment in 11 cases [13]. A second prospective study, including 55 children and adolescents with HL, showed, according to ^{18}F FDG PET images, an upstaging in 12,7% and a downstaging in 3,6% of cases [12].

More recently, comparing the integrated PET-CT and CECT in the evaluation of initial staging of HL, several reports confirmed the higher sensitivity of former technology, showing an upstage rate ranging from 14% to 28% and a downstage rate of about 6%, with changes in the treatment strategies in most of these patients [21–23].

Compared to previous studies, for the first time we were able to demonstrate the utility of PET-CT in the prognostication of localized HL. In fact, among these 29 cases, based on the PET-CT results, three patients were reclassified at unfavorable risk because of the higher number of involved nodal areas, and received a more intensive treatment than that indicated by the CECT.

In addition, a change in the treatment strategy was also observed in two additional cases, because of a PET-CT upstage.

However, the role of PET-CT in the staging work up is still considered “strongly recommended” but not mandatory, likely because CECT has a greater diffusion and a better standardization than PET-CT and because it is still considered preferable both in measuring the nodal areas and bulky disease and in radiation planning. As concerns these latter issues, herein we provide evidences that in patients with bulky disease, PET-CT was able to measure nodal areas similarly to CECT. With respect to the radiation planning, there are now several evidences showing that PET-CT, leads to a better implementation of the involved-node radiation therapy as reported by Girinsky et al. in a prospective multi-center study including 135 patients with HL and with indication to radiotherapy [30].

In conclusion, based on the fact that PET-CT is more sensitive than CECT and provides a baseline analysis against which to evaluate the early response to chemotherapy, we believe that, our present data, showing that PET-CT leads to a change in treatment strategy even in localized HL, support the issue that PET-CT should replace CECT in the staging procedures of HL.

Declaration of interest

None.

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