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research article

Negative predictive value of F-18-FDG coincidence PET in patients with Hodgkin's disease and a residual mass after therapy: a retrospective diagnostic test study

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Background. *The aim of the study was to asses the negative predictive value (NPV) of FDG-PET performed with triple-head coincidence gamma camera after the first-line therapy or salvage therapy in patients with Hodgkin's disease (HD) compared by a long-term follow-up as a reference standard.*

Methods. *This retrospective diagnostic test study was done at the University Hospital Centre Zagreb between June 2001 and February 2008. The charts of 131 consecutive patients with Hodgkin's disease were reviewed. Seventy-three consecutive PET-negative patients (median age 28 years; range 12-80 years) with primary or recurrent biopsy confirmed lymphoma after the first-line therapy or salvage therapy were followed-up at least 12 months (median 23 months; range 12-69 months). All already performed ^{18}F-FDG PET scans (using hybrid PET camera with triple head coincidence imaging capability within a few months after the completion of the therapy) were again visually interpreted by two board-certified nuclear medicine physicians who were blinded to any clinical or CT data. The negative predictive value of FDG-PET performed with triple-head coincidence gamma camera (Index test) was compared with a long-term follow-up as a reference standard.*

Results. *Out of 131 patients 73 turned-out to be PET-negative. Of those 73 PET-negative patients, 61 have been scanned after the first-line chemotherapy/radiotherapy, and only 3 of them relapsed in a follow-up (negative predictive value 0.95). Twelve patients with resistant disease have been scanned after the repeated therapy, and 4 of them relapsed in a follow-up period (negative predictive value 0.66).*

Conclusions. *This methodology with a triple-head coincidence gamma camera has a high negative predictive value. A negative PET scan can reassure patients and their doctors that the disease is not active.*

Key words: Hodgkin's disease; fluorine-18-fluorodeoxyglucose; FDG; PET; therapy monitoring; prognosis; follow-up; negative predictive value

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Introduction

Hodgkin's disease (HD) is a highly curable malignancy. With the modern therapy a disease-free survival is around 80% at 5 years.[1] However, HD survivors face significant medical problems related to toxicities of chemo- and radiotherapy, including secondary primary malignancies, cardiovascular and endocrine problems.[2] Therefore, avoiding an unnecessary therapy is very important.[3]

Accurate staging is essential for optimizing the patient's therapy but the main dilemma in assessing response at the end of the treatment is the presence of residual mass. In the large percentage of patients (> 60%) conventional imaging methods show remaining tumour masses at the end of the therapy, although only a small percentage of these patients still have the active disease and eventually will relapse.[1,4,5]

Computed tomography (CT) has long been the standard procedure for staging, therapy monitoring and follow-up of lymphoma patients, but it has well-known limitations, caused by the fact that the differentiation between normal and abnormal findings is based exclusively on lymph node size, and cannot differentiate scar tissue from viable tumour in the residual mass.[3,6,7]

Metabolic imaging using fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET provides a functional characterization of tissue and assesses tumour viability unrelated to morphologic criteria.[8,9] High accuracy of FDG-PET in characterization of residual masses and early detection of recurrent disease cause this imaging method to have an important role in the management of lymphoma by enabling a more precise and accurate determination of the disease status. The accurate assessment of response at the end of the therapy is of considerable prognostic importance because it can enable physicians to withhold the unnecessary additional radiotherapy or even high-dose chemotherapy and autografting and, thus, spare the patient's acute and late toxicity.

Numerous studies and two recent meta-analyses confirm a high negative predictive value (NPV) of FDG-PET performed using dedicated PET scanners in patients with HD.[4,10-12] The same is not true for positive FDG-PET findings and generally, in such cases a biopsy is recommended for the confirmation of presence of the active disease.[11-14]

It is well known that coincidence gamma cameras have inferior sensitivity for the tumour detection in comparison to dedicated PET scanners.[15,16] Therefore, some authors expressed doubts about the value of coincidence FDG-PET scanning for the response assessment in patients with lymphoma.[17,18]

The aim of this study was to asses the negative predictive value (NPV) of FDG-PET performed with a triple-head coincidence gamma camera after the first-line therapy or salvage therapy in patients with HD compared by a long-term follow-up as a reference standard.

Patients and methods

Design and setting

This retrospective diagnostic test study was done at the University Hospital Centre Zagreb between June 2001 and February 2008.

Patients

One-hundred thirty-one patients with a residual mass after the treatment of HD from our or collaborating centres had a FDG-PET scan performed at our centre. All patients had pre-therapy biopsy – proven HD. Initial staging consisted of a careful

clinical examination of peripheral lymph node areas, CT scanning of the thorax, abdomen and pelvis and a bone marrow biopsy. Those examinations that were positive prior to the treatment were repeated during restaging. Patients with a lymph node visible on a CT-scan bigger than 1.5 cm in the greatest diameter were considered to have a residual mass.[19]

Only the follow-up of 73 PET-negative patients was analyzed. In 61 patients the initial PET study was performed after the front-line therapy and in 12 after the salvage therapy. The follow-up of patients was at least 12 months (median 23 months; range 12-69 months).

FDG-PET

All PET studies were performed using IRIX hybrid PET camera (Philips Medical System, USA) with triple head coincidence imaging capability and equipped with parallel slat collimators. Its improved electronics for the coincidence detection allows the detectors to reject any events that normally would have caused pile-up and mispositioning. A detailed system description and performance characteristics are given elsewhere.[20,21]

About 370 MBq (10 mCi) of ^{18}F-FDG was administered intravenously to each patient after overnight fasting. Patients received a diuretic to minimize artefacts due to urinary stasis and were kept well hydrated. Between injection and scanning patients lied still to avoid FDG muscular uptake. Sixty minutes post injection two tomographic acquisitions of the neck, thorax, abdomen and groins were done, 30 min duration each, using angular step 3^0, with all three camera heads making full 360^0 rotation in rectangular configuration (heads 2&3 parallel to each other, head 1 perpendicular to heads 2&3). After the acquisition, raw list mode data were rebinned into SPECT-like projections (matrix: 128x128, zoom=1.0) using single slice rebinning algorithm (axial acceptance angle 12^0). The images were iteratively reconstructed. No attenuation correction was used.

Interpretation of ^{18}F-FDG PET scans

All already performed ^{18}F-FDG PET scans were visually interpreted again by two board-certified nuclear medicine physicians (D.H., with 9 years of FDG-PET experience; A.M. with 5 years FGD-PET experience) who were blinded to any clinical or CT data. A positive result was defined as the focal activity higher than that of surrounding background tissue not located in areas of physiological ^{18}F-FDG uptake, without similar activity seen on the contra lateral side. A negative result was defined as no abnormal ^{18}F-FDG uptake at any side.

Ethics

A signed informed consent for imaging and using the patient's data for the further research was obtained from all patients. The study was approved by the Ethics Committee of University Hospital Centre, Zagreb.

Statistical analyses

The values are expressed as negative predictive values (NPV) with 95% confidence intervals (CI) by using the exact binomial method.

Results

Out of total 131 patients 58 patients turned-out to be PET-positive, and were not included in the study. The demographic and clinical data of 73 PET-negative patients are presented in Table 1. Their median age was 28 years (range, 12-80 years). At diag-

nosis 3 patients were in stage I, 46 in stage II, 16 in stage III and 8 in stage IV. ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) was the most frequently used front-line treatment. Patients in stage I and II generally received 4 cycles of ABVD and involved-field irradiation and those in stage III and IV 6 to 8 cycles of ABVD. Patients who had a negative PET scan received no further antitumor therapy until relapse.

Flow diagram of our patients is presented in Figure 1. Seven patients (out of 73) relapsed (NPV = 0.90; CI: 0.81-0.96), three (out of 61 patients) after the front-line treatment (NPV = 0.95; CI: 0.86-0.99) and four patients (out of 12) after the salvage therapy (NPV = 0.67; CI: 0.35-0.90).

Table 1. Demographic and clinical characteristics of PET-negative patients with Hodgkin's disease (N=73)

Characteristics	Values
Median age (years)	28 (range 12-80)
Sex	
Male	36
Female	37
Histology	
Nodular sclerosis	52
Mixed cellularity	10
Lymphocyte rich	1
Not available	10
Ann Arbor clinical stage	
I	3
II	46
III	16
IV	8
B symptoms	
Yes	38
No	35
Treatment	
Chemotherapy alone	24
Chemotherapy and radiotherapy	49
Follow-up after PET (months)	
Median	23
Range	12-69

Discussion

The results show that FDG-PET performed in HD patients with a residual post treatment tumour mass using a triple-head coincidence gamma camera has a high NPV (0.90). This is especially true for front-line patients where it reaches 0.95. Thus, our results in these patients are comparable to results obtained with dedicated PET systems with NPVs between 0.90 and 0.96.[4,7,10,22] Lower NPV (0.66) in patients receiving salvage therapy can be expected because of a more aggressive disease course.

We have decided not to analyze the PET positive patients in detail because, after scanning, they were not treated in a uniform way. Thus, it would be very hard to discern the true positive predictive value of a positive PET scan. Furthermore, we are missing gold standard (biopsy) for the really active disease. Besides, because of physiological variants, false-positive FDG uptake is predominantly due to post-therapy inflammatory changes, which subsequently resolve.[23,24] The body of evidence about false positive post treatment PET in patients with HD is constantly growing,[12-14,18] and to gain accurate data FDG-avid lesions must be checked by biopsy, specially in previously unaffected region.[3,4,10,12-14,18,23,25] Noninvasive alternative is to wait and repeat PET imaging in one or two months.[24]

This study has several limitations including a retrospective design, relatively small sample size reflecting the low incidence of HD and aggregation of patients with varying disease stages and treatment regimens. The PET equipment used was outdated lacking attenuation correction. Still, the high NPV indicates that coincidental PET scanning might be as reliable as dedicated PET or PET/CT systems, at least in patients with HD with a residual mass after the ini-

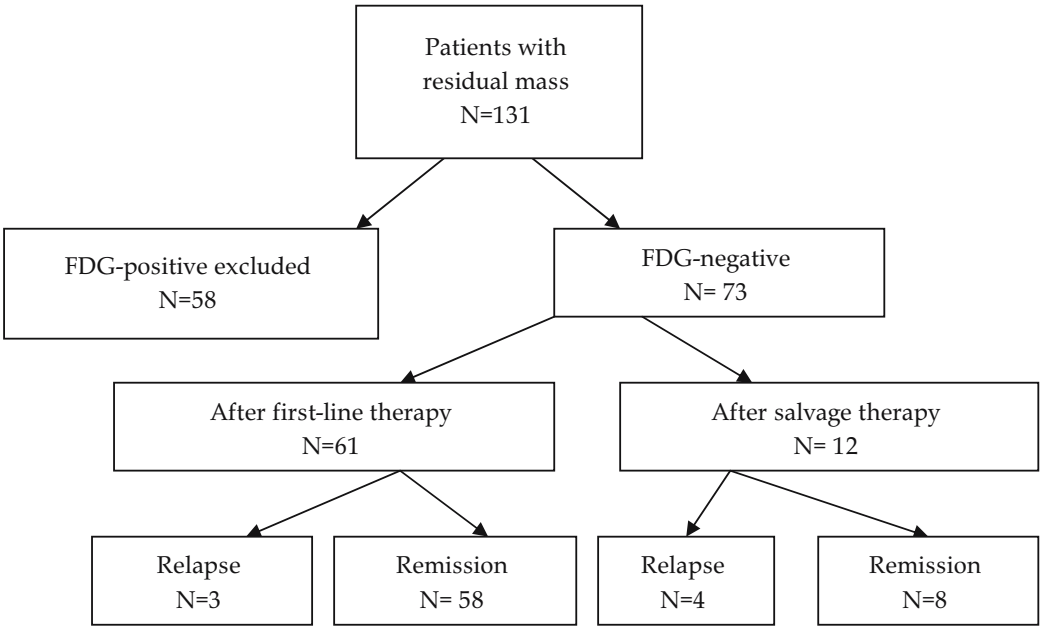

Figure 1. The flow diagram of primary or recurrent Hodgkin's disease (HD) patients with residual mass and FDG-PET scan after first-line or salvage therapy.

tial therapy. This means that coincidence PET can be a viable alternative for those centres which do not have an easy access to dedicated PET or PET/CT systems, which is wildly used.[8] In this constellation is a negative PET scan an important contribution in the management of patients and can provide reassurance to both, patients and their doctors, that disease is not active.

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