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# COMPARISON OF $^{18}$F-FDG POSITRON EMISSION TOMOGRAPHY AND COMPUTED TOMOGRAPHY IN PATIENTS WITH COLORECTAL CARCINOMA AND LYMPHOMA: OUR INITIAL CLINICAL EXPERIENCE

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SUMMARY – Findings obtained by fluorine-18-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) and computed tomography (CT) were compared in patients with malignant lymphoma and colorectal carcinoma. In 14 malignant lymphoma patients, 16 $^{18}$F-FDG PET procedures were performed to assess chemotherapy and/or radiotherapy outcome (remission). One patient with clinically overt relapse of non-Hodgkin's lymphoma underwent PET to assess disease dissemination prior to prescribing second-line chemotherapy. Two patients were submitted to PET on two occasions. PET pointed to residual disease in six of 14 patients and was inconclusive in one patient. These patients underwent computed tomography (CT), some of them before and others after PET examination. Then PET and CT findings were compared and therapeutic response, i.e. disease remission was assessed. The signs of residual disease were present in four and absent in nine patients, whereas inconclusive findings in terms of residual disease were recorded in one patient. Although our initial clinical experience was acquired in quite a small number of patients, CT modified clinical evaluation of residual disease in two patients and should be included along with PET in diagnostic work-up of these patients.

Key words: *Intestinal neoplasms – diagnosis; Intestinal neoplasms – pathology; Colorectal neoplasms – pathology; Lymphoma – diagnosis; Lymphoma – therapy; Colorectal neoplasms – radiography; Radiopharmaceuticals – diagnostic use*

## Introduction

Fluorine-18-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) is one of the most rapidly developing diagnostic methods in nuclear medicine. FDG is a glucose analog that has found application in oncology, neurology and cardiology as a universal radiopharmaceutical. In clinical practice, $^{18}$F-FDG is mainly used in oncology. The examination is based on greater radiopharmaceutical uptake by malignant tumors with high metabolic activity compared with the surrounding tissue. However, it is not only tumor cells that show an increased $^{18}$F-FDG uptake, since inflammatory cells like neutrophils, activated macrophages and endothelial cells also exhibit enhanced $^{18}$F-FDG uptake. Therefore, increased $^{18}$F-FDG uptake may also be observed in normal and non-malignant conditions such as infection, inflammation or tissue healing[1].

$^{18}$F-FDG PET has been adopted as a useful tool in tumor detection, disease staging and assessment of therapeutic response in many malignant tumors, lymphoma in particular, lung carcinoma, colorectal carcinoma, head and neck carcinoma, breast cancer and melanoma[2-4]. The overall method sensitivity and specificity have been estimated to 84% and 86%, respectively. Many studies report on PET to be more reliable in the assessment of

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disease stage and post-therapeutic remission than currently used conventional methods[3,4]. PET sensitivity exceeds that of conventional computed tomography (CT) by 10%-15%, along with comparable specificity[1]. Schwaiger and Wieder report on PET to have modified disease staging in 15%-18%, and according to Kostakoglu *et al.* in as many as 41% of patients with malignant lymphoma[1,3].

PET has a number of advantages over other diagnostic methods in tumor detection. Many carcinomas are systemic disease, and whole body imaging by $^{18}$F-FDG PET allows for simultaneous assessment of the disease dissemination and progression. It also enables earlier tumor detection because biochemical changes in tumor tissue precede morphological ones, which then are potentially detectable by other methods such as CT and magnetic resonance imaging (MRI).

In patients with non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL), accurate staging is crucial for appropriate choice of therapy and reduction of morbidity associated with chemotherapy and/or radiotherapy toxicity. Proper choice of therapy will influence the patient's quality of life both during and after therapy completion. Correct assessment of therapeutic response (remission) after first-line therapy is of utmost importance in NHL and HL, both for prediction of disease relapse and for earliest possible introduction of second-line therapy while tumor growth has not gone too far[1,4].

The key question is whether the modification in disease staging will lead to change in therapeutic approach and disease outcome. Schwaiger and Wieder believe that PET should be done in all HL patients, those with clinical stages I and II in particular, where modification of disease staging influences the choice of therapy, and in patients with aggressive NHL to assess therapeutic response, while it is not generally indicated in indolent lymphomas due to the high rate of false-negative findings on therapeutic response evaluation[1]. The Working Group for Standardization and Interpretation of PET in Lymphomas[6] has proposed the following indications for PET: for predictably FDG-avid (PA) and potentially curable disease, such as diffuse B-large cell lymphoma and HL, PET is desirable but not necessary on disease staging, as it will better define the seats of disease, and on their restaging; on staging of indolent lymphomas, PET is only indicated if the final goal is assessment of therapeutic response. In other malignant tumors, PET has also found application in the assessment of therapeutic response, search for primary tumor in metastatic disease, and evaluation of a lymph node or other tissue malignant/benign behavior.

CT is an important tool in the routine work-up for patients with malignant lymphomas on making the diagnosis, staging, restaging, and assessment of disease remission following chemotherapy and/or radiotherapy. The International Workshop Criteria for evaluation of therapeutic response in NHL are based on CT finding, along with bone biopsy, laboratory and clinical data[7]. However, CT suffers from a number of limitations since interpretation of a lymph node tumor involvement relies on anatomical criteria of the node size and appearance. The limitations are primarily caused by the CT inability to differentiate between viable tumor and fibrosis in residual tumor in patients with complete remission according to clinical evaluation, which is recorded in some 40% of NHL patients treated by chemotherapy/radiotherapy[7].

PET can differentiate viable residual disease from benign post-therapeutic lesions or other causes of lymph node enlargement with high precision, and can therefore influence therapeutic modification; the more so, PET can help identify those patients that require adjuvant therapy or modification of therapeutic protocol[5,8].

## Patients and Methods

All malignant lymphoma patients were treated by polychemotherapy at Department of Medicine, Dr. Josip Benčević General Hospital in Slavonski Brod, Croatia. Patients with colorectal carcinoma were operated on at Hospital Department of Surgery, followed by chemotherapy administered at Department of Medicine. One patient with rectal carcinoma was referred for radiotherapy to University Hospital for Tumors in Zagreb. Six weeks after chemotherapy and/or radiotherapy, patients underwent $^{18}$F-FDG PET at Department of Nuclear Medicine, Radiation Protection and Pathophysiology, Osijek University Hospital in Osijek, Croatia, using GE Medical Systems PET Advance Nxi 40 min p.i. (OSEM). Due to the procedure unavailability, PET could not be performed at the time of diagnosis, i.e. before therapy, in any of our patients. CT was performed at Department of Radiology, Dr. Josip Benčević General Hospital in Slavonski Brod, using a Siemens Somaton Emotion Duo device. Basic patient clinical characteristics are shown in Table 1.

*Table 1. Patient clinical data*

| Patient No./Initials | Age (yrs) | Sex (M/F) | Diagnosis | Histopathology | ChT | RT |
|---|---|---|---|---|---|---|
| 1 T.D. | 21 | M | Hodgkin's lymphoma | Nodular sclerosis type II | + | + |
| 2 D.S. | 31 | F | Hodgkin's lymphoma | Classic mixed cellularity | + | + |
| 3 G.V. | 41 | F | Non-Hodgkin's lymphoma | Nasal NK/T-cell lymphoma | + | + |
| 4 R.M. | 52 | M | Non-Hodgkin's lymphoma | Marginal zone | + | – |
| 5 Z.K. | 68 | F | Non-Hodgkin's lymphoma | Follicular centrocytes | + | – |
| 6 S.M. | 66 | M | Non-Hodgkin's lymphoma | Marginal zone | + | – |
| 7 Š.B. | 28 | M | Colorectal carcinoma | Adenocarcinoma | + | – |
| 8 F.H. | 41 | M | Colorectal carcinoma | Adenocarcinoma | + | – |
| 9 Č.A. | 58 | M | Colorectal carcinoma | Adenocarcinoma | + | + |
| 10 Č.L. | 57 | M | Colorectal carcinoma | Adenocarcinoma | + | – |

Nasal NK/T-cell lymphoma = nasal natural killer/T-cell lymphoma; ChT = chemotherapy; RT = radiotherapy

$^{18}$F-FDG PET was performed in 14 patients, i.e. six patients with colorectal carcinoma and eight patients with malignant lymphoma (two with HL and six with NHL). Two patients (T.D., male, HL, and G.V., female, NHL) underwent PET on two occasions, i.e. after chemotherapy when the finding pointed to residual disease; then the patients received radiotherapy, followed by control PET. In 13 of 14 patients, PET was done after chemotherapy or chemo-/radiotherapy for assessment of therapeutic response or remission in patients with malignant lymphoma; one patient with disease relapse underwent PET for assessment of disease dissemination, prior to prescribing second-line chemotherapy.

## Results

CT and $^{18}$F-FDG PET findings in our patients are presented in Table 2. After chemotherapy, PET finding was positive, pointing to residual disease in eight patients, negative in five patients, and inconclusive in one patient. Two of the eight patients with positive post-chemotherapy PET finding received radiotherapy and then underwent control PET, now with negative finding. CT showed positive finding in six patients, negative finding in seven patients, and inconclusive finding in one patient (the same with dubious PET finding). In two patients that underwent additional radiotherapy, control CT also showed negative finding.

*Table 2. Computed tomography (CT) and fluorine-18-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) results in our patients*

| CT/PET | PET + | PET – | PET +/– | Total |
|---|---|---|---|---|
| CT + | 2 | 0 | 0 | 2 |
| CT – | 2 | 5 | 0 | 7 |
| CT +/– | 0 | 0 | 1 | 1 |
| Total | 4 | 5 | 1 | 10 |

In 13 of 14 patients, PET was performed for re-evaluation and post-therapeutic assessment of remission. One patient with clinically overt relapse of malignant lymphoma underwent PET for assessment of the disease dissemination prior to prescribing second-line chemotherapy, so comparison of PET and CT findings was done in 13 patients. In 11 of these 13 patients, the findings obtained by the two methods were concordant (negative PET and CT in seven patients, positive PET and CT in three patients, and dubious PET and CT in one patient). Discrepancy of PET and CT findings was observed in two patients (positive PET and negative CT), both with colorectal carcinoma (descending colon carcinoma in one patient). A solitary hypermetabolic lesion of upper mediastinum was verified by PET, and the patient underwent CT of the thorax which showed it to be the thymus, not a tumor mass in the mediastinum. In the other patient with transverse colon carcinoma, a solitary focal pathologic activity accumulation visualized on CT in the subdiaphragmal region laterally on the left was interpreted as the small intestine curvature blockade, probably due to postoperative cicatricial lesion. The patient with dubious PET and CT findings suffered from rectal carcinoma and had undergone pelvis minor radiotherapy; therefore it was quite difficult to differentiate between residual disease and reactive postoperative and post-irradiation lesions. The patient's clinical finding, laboratory tests and tumor markers were normal. As 36 months had elapsed from operative procedure, we were inclined to rule residual disease out. In a female HL patient both PET and CT definitely indicated residual disease, however, the localization of residual disease varied and was therefore difficult to confirm. The diagnosis of stage IIB HL (of the neck and mediastinum) was made in April 2004. The patient had received chemotherapy followed by radiotherapy of the mediastinum. Residual disease was now visualized on PET as a hypermetabolic lesion in posterior mediastinum, where it was not observed on CT staging, but was only visualized in anterior mediastinum. The patient felt well, was free of symptoms, and had normal laboratory, ESR, LDH and Cu findings.

## Discussion

In the treatment of malignant lymphoma, staging of the disease is of utmost importance for appropriate choice of therapeutic protocol in each individual patient. However, re-evaluation and assessment of therapeutic response upon chemotherapy and/or radiotherapy completion is no less important. CT remains a standard tool on both staging and restaging patients with malignant lymphomas. In the last few years, PET has been increasingly employed in staging and restaging these patients[5,9-12], thus a new definition of complete remission, partial remission, progressive disease and stable disease has been proposed, while the term ‘unverified complete remission’ has been abandoned[4,6]. Some studies have shown the specificity and sensitivity of PET to considerably exceed those of CT, therefore questioning the need of the latter[3,13]. We also posed the same question, although PET is not readily available in our setting, and the number of patients was small, thus precluding any reliable statistical analysis. Yet, our patient population, although small, clearly showed the reliability of CT to be comparable to PET, while dubious PET finding remained so on re-evaluation; PET was found to be most reliable in case of negative finding, and cicatricial and inflamed tissue inaccessible to sampling for histopathologic verification remains a problem for the clinician. We consider that PET should be performed on both staging and restaging in patients with HL, stage I and II in particular, and in those with diffuse large-cell lymphoma. If PET had been available to our patients, perhaps we would not have faced a dilemma whether or not residual disease developed in our female HL patient. Based on their results, Reinhardt *et al.* also prefer comparison of CT and PET findings on predicting disease progression as well as in post-therapeutic evaluation[11]. Juweid and Cheson found a combined use of the international prognostic index and PET in patients with malignant lymphomas to be superior to either CT or PET alone in discriminating patients with complete remission/unverified complete remission from those with partial remission, whereas patients with partial remission or stable disease should be considered as having persistent disease requiring additional therapy[8].

We consider that negative PET is of great value in patients with colorectal carcinoma, for a number of reasons. PET is simpler, less invasive and less discomfortable for patient than colonoscopy. The latter may frequently be difficult or even impossible to perform due to postoperative and post-irradiation adhesions and stenosis, leaving the clinician in a dilemma whether or not a disease relapse has occurred. Furthermore, some patients suffer occasional abdominal colics and a picture of subileus after operative procedure, chemotherapy and/or radiotherapy, and negative PET may help decide on conservative or surgical therapy, then assisting the surgeon in preparing the operative procedure (negative PET most likely suggesting adhesions or benign stenosis, and positive PET pointing to the underlying disease relapse).

## Conclusion

Comparison of CT and PET findings makes assessment of remission in patients with malignant lymphoma more reliable than either study alone. PET is highly valuable when yielding a negative finding, and is superior in the groups of patients defined as unverified complete remission and partial remission. In addition, PET is more precise on planning the irradiation area. In our opinion, CT remains a necessary tool in the diagnostic and post-therapeutic work-up for malignant lymphoma and other tumors. In our small patient sample, CT pointed to two false-positive PET results in patients with colorectal carcinoma. However, considering relative unavailability of PET in our setting, priority in referring for PET study should be given to patients with residual tumor mass on CT scan and those with stage I and II HL on both staging and restaging.

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## Sažetak

## USPOREDBA $^{18}$F-FDG POZITRONSKE EMISIJSKE TOMOGRAFIJE I KOMPJUTORIZIRANE TOMOGRAFIJE U BOLESNIKA S KOLOREKTALNIM KARCINOMOM I LIMFOMOM: NAŠA POČETNA KLINIČKA ISKUSTVA

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Usporedili smo nalaze fluoro-18-fluorodeoksiglukoza (FDG) pozitronske emisijske tomografije ($^{18}$F-FDG PET) i kompjutorizirane tomografije (CT) u bolesnika s malignim limfomom i kolorektalnim karcinom. U 14 bolesnika $^{18}$F-FDG PET je učinjen 16 puta radi procjene ishoda kemoterapije i/ili radioterapije, odnosno remisije. U jednog bolesnika s klinički jasnim recidivom ne-Hodgkinova limfoma PET je proveden radi procjene proširenosti bolesti prije ordiniranja druge linije kemoterapije. U dvoje bolesnika PET je učinjena dva puta. U šestoro od 14 bolesnika nalaz PET ukazivao je na rezidualnu bolest, dok je u jednog bolesnika bio dvojben. Stoga je u tih bolesnika učinjena i CT; u nekih bolesnika CT je izvedena prije PET, a u drugih nakon PET. Tada smo usporedili nalaze PET i CT te procijenili terapijski odgovor, tj . remisiju bolesti. Znaci rezidualne bolesti bili su prisutni u četvoro bolesnika, odsutni u devetoro bolesnika, dok je kod jednog bolesnika i dalje bilo nejasno je li rezidualna bolest prisutna ili nije. Iako se ovo naše početno kliničko iskustvo odnosi na mali broj bolesnika, CT je promijenio kliničku procjenu rezidualne bolesti u dvoje bolesnika i smatramo da bi uz PET i CT trebao biti sastavni dio dijagnostičke obrade takvih bolesnika.

Ključne riječi: *Crijevne novotvorine – dijagnostika; Crijevne novotvorine – patologija; Kolorektalne novotvorine – patologija; Limfom – dijagnostika; Limfom – liječenje; Kolorektalne novotvorine – radiografija; Radiofarmaceutici – dijagnostička primjena*