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Oral Communications

ONCOLOGY 1 – BRAIN, HEAD AND NECK

Influence of ^{11}C-methionine PET in radiotherapy planning of primary brain tumors

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Background and aim ^{11}C-methionine PET (MET-PET) is a well-established tool for the assessment of primary brain tumors. The tracer itself is capable of delineating tumor extent more reliably than other conventional imaging modalities, including MRI, which has long been considered the reference standard in tumors of this type. These findings paved the way for increasing use of MET-PET also in target volume delineation before radiotherapy (RT). To date, few research groups have investigated the differences in treatment volumes determined by PET and MRI/CT, and only one has sought to correlate findings with patient outcomes. Thus, the aims of this study were to assess the clinical impact of MET-PET on RT planning of primary brain tumors, and to evaluate how treatment modification might influence the outcome of patients.
Materials and methods We analyzed data deriving from 31 consecutive patients (M:F=20:11; mean age 53 years) affected by pathologically proven gliomas and referred to our institute for RT planning. All patients had undergone dedicated brain MRI, CT and MET-PET in order to define gross tumor volumes (GTV): GTV-MRI/CT, outlined on co-registered and fused CT and MR images, and GTV-PET, determined by areas with pathological MET uptake. The different volumes were compared and the results analyzed with respect to treatment modification and impact on patient outcomes. In 19 patients, we were able to perform a post-treatment evaluation that helped to define the disease outcome. For analysis purposes, we also calculated the progression-free (PFS) and overall survival (OS) of patients, with a mean follow-up of 5.4 months.
Results In our cohort, MET-PET was positive in 29/31 patients (94%) in whom we were able to define a GTV-PET. The mean volume of the lesions on PET was 18.33cc (range 0-74.92 cc), whereas the mean GTV-MRI/CT was 65.93cc (range 8.54-165.58 cc). In all cases, the GTV-MRI/CT was larger than the GTV-PET, but in 20 cases (64.5%) the extent of the tumor according to PET prompted modification of the treatment planning. The mean percentage of added volume after MET-PET was 9.24%, which ranged from -29.4% (overall treatment volume reduced by almost 1/3) to +37.8%. In 19 patients, undergoing an instrumental check after RT, we compared the impact of treatment modification and other predictive factors on PFS and OS, and found treatment modification on the basis of MET-PET to be the only significant predictor of both PFS (p=0.018) and OS (p=0.003). No other factor (age, histology, multifocality, relapse/primary, treatment, uptake) was correlated with PFS and OS.
Conclusions As expected, MET-PET shows a significant impact on radiotherapy planning of patients presenting with primary brain tumor. In our study, treatment modification according to PET results influenced patient outcomes and seemed to be the only predictor of longer PFS and OS.

Is there a role for dual-point brain ^{18}F-fluoro-ethyl-tyrosine PET/CT in evaluating suspected glioma recurrence?

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Background Although ^{18}F-fluoro-ethyl-tyrosine (FET) has been shown to be useful for diagnosing brain tumor recurrence, the evaluation of FET uptake in operated and radiotreated patients presents some criticisms in differentiating recurrence from post-treatment changes. On the other hand, FET uptake dynamic analysis, with decreasing late uptake in high-grade and increasing late uptake in low-grade gliomas, could be an adjunct tool for the evaluation of these patients.
Aim In view of these issues, we performed dual-time point brain FET-PET/CT in previously treated gliomas with suspected recurrence, in order to retrospectively evaluate the role of early and late FET uptake in orienting diagnosis and predicting outcome.
Patients and methods From November 2011 to April 2012, 18 patients (median age 50 years) with surgically +/- radiotreated gliomas (7 WHO low-grade, and 11 WHO high-grade anaplastic gliomas or glioblastomas), with clinical or MRI suspected recurrence, were submitted to brain FET-PET/CT (GE Discovery LS) in order to obtain a metabolic assessment of residual post-treatment disease. A visual and semi-quantitative evaluation (SUVmax and tumor-to-background ratio) were obtained by two skilled nuclear medicine physicians, in agreement, 5-10 min. (early) and 30-40 min. (late) after i.v. injection of 150-185 MBq of ^{18}F-ethyl-tyrosine. Delta SUVmax (late SUVmax – early SUVmax/early SUVmax) and delta tumor-to-background (T/B) ratio were then calculated. Histopathological evaluation was obtained in two patients, and a median seven-month follow-up in the others.
Results Nine out of 22 brain suspected lesions were considered as relapse at FET-PET/CT on the basis of distribution and quantification of FET uptake (SUVmax and/or T/B ratio > 2) at late PET/CT, 7 true positive by mean of histology and follow-up and 2 false positive (1 meningioma, 1 post-treatment changes). On the other hand, 13 suspected lesions were considered late FET-PET/CT negative for relapse, 6 true negative and 7 false negative. At dual-time point evaluation, lesion delta SUVmax and delta T/B ranged respectively from -22% to +33% and from -30% to +24% in patients with improved or stable disease, and from -19% to +18% and from -63% to +16% in patients with progressive disease or dead at follow-up. In spite of this spread variability between lesions, delta SUVmax evaluation could have correctly recognized as relapse 3 out of 7 FN lesions in the single late evaluation, one glioblastoma recurrence with low but decreasing SUVmax (delta SUVmax-19.7%) and two low-grade glioma recurrence with increasing SUVmax (delta SUVmax +18.6%).

Conclusions Our preliminary data confirm some pitfalls in FET-PET/CT evaluation of surgically and/or radiotreated gliomas because of treatment-induced changes interference. Visual analysis of FET uptake distribution seems to remain the best assessment criterion for suspected glioma relapse. A high (>2) SUVmax and T/B ratio at 30-40 min imaging are probably related to recurrent disease, but a lower FET uptake seems to have a poor negative predictive value. On the other hand, SUVmax course over time presents too much overlapping among lesions to constitute a valid reference parameter, although it may be useful in single doubtful cases considering the different uptake behaviour of low- and high-grade gliomas. Nevertheless, further studies are necessary to confirm this impression.

Predicting relapse of previously treated gliomas using ^{18}F-DOPA PET/CT

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Background L-3,4-dihydroxy-6-[^{18}F]fluorophenylalanine (F-DOPA) is an aminoacid PET tracer, which can be successfully exploited for imaging and grading newly diagnosed gliomas. In previously treated gliomas, however, F-DOPA uptake fails to predict tumor grade and proliferation. We conducted a pilot study to assess whether F-DOPA can help to prognosticate short-term recurrences in previously treated gliomas.

Materials and methods Between July 2010 and August 2012, 34 patients with previously treated gliomas underwent F-DOPA brain PET/CT at Sant'Andrea Hospital in Rome, in addition to conventional magnetic resonance (MR) surveillance. Static images of the brain were acquired on a Philips Gemini camera over a 20-minute period, starting 15 minutes after the i.v. injection of 185 MBq F-DOPA. A low-dose CT scan was used for attenuation correction. PET images were classified as positive (SUVmax >2), mildly positive (SUVmax <2) or negative by three nuclear medicine physicians, aware of clinical data. Semi-quantitative uptake parameters (i.e. SUVmax, tumor-to-contralateral background ratio, tumor-to-contralateral basal ganglia uptake) were also recorded. Because of the exploratory nature of the study, subsequent clinical decisions were based on clinical judgment and radiological findings only, without taking into account the PET results. MR scans preceding (pre-MR) and following (post-MR) the PET study were retrospectively scored according to the RANO criteria by two radiologists in consensus, blinded to patient information. In the event of PET positivity, patterns of relapse were studied by fusing F-DOPA PET/CT with post-MR on a HERMES workstation. Appropriate statistical analysis was performed to identify factors possibly differentiating between early relapsing and stable patients.

Results Thirty-four patients with previously treated low- (n=14) or high-grade (n=20) gliomas were enrolled. Prior treatments included various combinations of surgery (32/34 pts), radiation therapy (26/34 pts) and chemotherapy (25/34 pts); 21 out of 34 patients had received all treatments. Chemotherapy was still ongoing in 14 patients. The median time elapsing between pre-MR and PET was 22 days (range: 1-180 days), while the median time between PET and post-MR was 60 days (range: 3-200 days). Overall, median follow-up after F-DOPA PET was 7 months (range: 2-27 months). F-DOPA PET was positive in 24 (70%) patients, mildly positive in 6 (18%), and negative in 4 (12%) patients. None of the patients with mildly positive or negative PET progressed. Fifteen out of 24 (62%) patients with positive PET were stable at first post-MR, while 9/24 (38%) progressed. Three additional patients showed clear signs of progression on a subsequent MR. Median SUVmax was 3.2 (range: 2.5-4.6) and 3.4 (range: 2.5-4.4) in stable and progressive patients, respectively. None of the semi-quantitative parameters under study was able to differentiate between early relapsing and stable patients, nor were any of the pre-PET characteristics recorded (all p>0.5). Nevertheless, the pattern analysis showed that the vast majority of progressions included areas of increased F-DOPA uptake. In particular, there was excellent correspondence between contrast enhancement and F-DOPA uptake, but radioactivity was also seen in non-enhancing areas. Interestingly, four PET-positive patients without contrast enhancement on pre-MR showed anaplastic progression within 8 months.

Conclusions In previously treated gliomas, the presence of significant F-DOPA uptake (SUVmax>2) does not necessarily imply a very early relapse. However, areas of progression are generally identified within the field of F-DOPA increased uptake, irrespective of contrast enhancement on pre-MR. Longer follow-up is needed to evaluate delayed relapses, and the potential predictive role of F-DOPA PET warrants further investigation especially in the subgroup of patients with a relatively good outcome.

Target volume delineation in patients with head and neck (H&N) cancer: impact of ^{64}Cu-ATSM vs FDG PET/CT

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In the last years functional imaging modalities such as FDG PET/CT have been used to increase the accuracy of target volume delineation. More recently a new tracer has been developed to detect intratumoral hypoxic areas, since hypoxia is known to be one of the most important factors of tumor resistance to radiotherapy (RT). This tracer is ^{64}Cu-ATSM.

The aim of this study was to conduct a preliminary assessment of the efficacy of ^{64}Cu-ATSM, in comparison with FDG, as a prognostic factor of response to therapy in H&N cancer patients who are candidates for RT.

Eleven patients (2 females and 9 males) affected by histologically proven H&N cancer and candidates for RT as first-line therapy were enrolled. All the patients underwent FDG PET/CT and ^{64}Cu-ATSM PET/CT within one week.

Biological target volume was calculated on both FDG and ^{64}Cu-ATSM PET/CT using a dedicated software on a dedicated workstation (V-CAR on Advantage, GE). The cutoff for delineating the volume was 45% of the SUVmax. The response to RT was assessed by FDG PET/CT performed approximately three months after therapy.

Ten patients presented significant uptake of both tracers. Five patients had FDG and ATSM positive node metastasis. One patient had FDG positive/ATSM negative node metastasis. One patient had FDG negative/ATSM positive node metastasis. One patient did not show ^{64}Cu-ATSM uptake in the primary cancer. There was no significant difference in biological target volume calculated with FDG (mean 13ml) versus ^{64}Cu-ATSM (mean 12ml) (Wilcoxon test, p=0.89).

The sensitivity and specificity in predicting the complete response to therapy calculated with ROC curves were: ATSM (ml) 100%, 40%, cutoff <49.4; ATSM (SUVmax) 83%, 40%, cutoff <2.3; FDG (ml) 83%, 60%, cutoff <28.5; FDG(SUVmax) 66.7%, 60%, cutoff <11.8.

ATSM PET/CT showed higher sensitivity than FDG PET/CT in predicting a complete response to therapy when considering the volume of tracer uptake, while FDG PET/CT showed a higher specificity. The ATSM SUVmax was also more predictive of a complete response after RT compared with FDG SUVmax.

These very preliminary results confirm that ATSM PET/CT is useful in the investigation of H&N cancer, and above all the detection of large

areas of hypoxia within the tumor and/or its metastasis is a strong negative prognostic factor for a complete response to RT.

Prognostic value of pre-therapy ^{18}F-FDG PET/CT for the outcome of radiotherapy treatment in patients with head and neck cancer

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Aim To evaluate the predictive role of pre-therapy ^{18}F-FDG PET/CT for the outcome of patients with Head and Neck Cancer undergoing radiotherapy treatment
Materials and methods We retrospectively included 19 pts (15 men and 4 women, mean age 59.2 yrs, range 23-81 yrs). Tumor sites were as follows: oropharynx in 12 (63.1%), rynopharynx in 5 (26.3%) and larynx in 2 (10.5%) . Twelve (63.1%) pts were in stage IV, 3 (15.8%) in stage III, 3 (15.8%) in stage II and 1 (5.3%) in stage I. All pts underwent FDG PET/CT before treatment with simultaneous integrated boost intensity-modulated radiotherapy guided by biological target volume defined on PET/CT images (BTV-SIB-IMRT). The median follow-up was 19.3 months (range 4 - 24). The prognostic role of different FDG PET uptake indexes (metabolic tumor volume-MTV, SUVmean and total lesion glycolysis -TLG) was assessed, using ROC analysis, considering 2-year disease free survival (DFS), local relapse free survival (LRFS) and distant metastasis free survival (DMFS). SUVmean and TLG were used with and without correction for partial volume effect (PVC).
Results A MTV cut-off value could divide the whole population into two groups, with MTV lower and higher than 32.4cc, characterized by different survival: DFS was 73.3 vs 25% ($p<0.025$), LRFS was 80 vs 25% ($p<0.01$) and DMFS was 93.3 vs 37.5% ($p<0.01$), respectively. A SUVmean cut-off value could separate the whole population into two groups, with SUVmean lower and higher than 10.8, characterized by DFS of 90 vs 33.3% ($p<0.025$), LRFS of 90 vs 44.4% ($p<0.05$) and DMFS of 90 vs 77.7% ($p>0.05$), respectively. When PVC was applied, DFS was 91 vs 25% ($p<0.01$), LRFS was 91 vs 37.5% ($p<0.025$) and DMFS was 91 vs 75% ($p>0.05$), with SUVmean lower and higher than 13.3, respectively. A TLG cut-off value of 469.8 g had the highest degree of significance in dividing the population in groups, with TLG below and higher than 469.8 g, characterized by DFS of 70.6 vs <1% ($p<0.001$), LRFS of 76.5 vs <1% ($p<0.001$) and DMFS of 94.1 vs <1% ($p<0.001$), respectively. When PVC was applied, 547.3 g TLG cut-off value could equally divide the population and the figures.
Conclusions MTV and TLG demonstrated a prognostic value in predicting DFS, LRFS and DMFS in our series of patients. SUVmean was only able to predict DFS and LRFS. When PVC was applied the uptake indexes clustered the patients with higher degree of statistical significance.

ONCOLOGY 2 – LUNG

Deep inspiration breath-hold [^{18}F]FDG PET/CT on 4-ring scanners in evaluating lung lesions: preliminary results

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Background [^{18}F]FDG PET/CT is an important nuclear medicine imaging tool for the diagnosis, staging, restaging, therapy monitoring and radiotherapy planning of malignant lesions, in particular those located in lungs. However, the CT scan is acquired during a single phase of the breathing cycle, whereas the PET scan acquisition occurs over many breathing cycles for the same length of CT scan. This discrepancy in acquisition may introduce misalignment between PET and CT images. When a misalignment is present, the quantification of the standardized uptake value (SUV), an important parameter in lesion evaluation, is inaccurate due to the incorrect attenuation correction map obtained from the CT scan. Furthermore, respiratory motion blurs PET images, leading to an overestimation of tumor volume, degrades the contrast and interferes with SUV evaluation, resulting in reduced PET/CT accuracy. One possible solution to misalignment and blurring is the deep inspiration breath-hold (DIBH) PET/CT technique. Since previous studies were affected by a low sensitivity due to the use of different scanner types, it seemed challenging to perform a study to investigate the feasibility and advantages of DIBH technique using a 4-ring PET/CT scanner, which allows increased sensitivity. We therefore performed a phantom study to determine the minimum breath-hold time to obtain a minor statistical error; subsequently, a clinical study was performed, to evaluate the improvement of image contrast for clinical purposes.
Methods The minimum breath-hold time was determined by a phantom study prior to the clinical study. Twenty-five patients with pulmonary lesions underwent a standard whole-body [^{18}F]FDG PET/CT scan in free breathing (FB), followed by a 20s single thorax PET/CT acquisition in DIBH. Lung lesion displacement between PET and CT images, lesion maximum standardized uptake value (SUV_{max}), mean standardized uptake value (SUV_{mean}) and volume, both in FB and DIBH PET/CT scans, were recorded. The percentage difference in SUV_{max} between the FB and DIBH scans was calculated and defined as the %BH-index.
Results An optimal acquisition time of 20s was determined by the phantom study. Twenty-three of the 25 patients completed the PET/CT acquisition in DIBH. Overall 27 lesions in 23 patients were studied. Two of the 25 patients were unable to hold their breath for an adequate time. In 19/27 lesions misalignment between PET and CT images in FB was found. PET/CT in DIBH showed a significant reduction of misalignment and an increase in SUV_{max} compared to FB. A correlation between the %BH-index and lesion displacement between PET and CT images in FB was demonstrated, significantly higher for lesions with a displacement > 8mm. As regards lesion location, differences were more evident for those located in the lower lobe than in the upper lobe.
Conclusions Better alignment between PET and CT lung lesion images is obtained by a 20-s DIBH PET/CT scan than by a FB scan, resulting in more accurate evaluation of lesion location, SUV_{max} and SUV_{mean}, especially for small lesions in the lower lung lobes. Given the great advantages and the minor limitations of this technique, if a 4-ring PET/CT scanner is available, we suggest to use it whenever there is evidence of misalignment between PET and CT images.

Two-year survival prediction in patients with stage I and II non-small cell lung cancer utilizing ^{18}F-FDG PET/CT SUV quantification

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Aim In non-advanced non-small-cell lung cancer (NSCLC), TNM stage is still the most reliable predictor of outcome after surgery. However, many patients in stage I or II may experience a worse outcome than expected and an early relapse even after a successful tumor resection. Magnetic resonance imaging (MRI), computed tomography (CT) and endobronchial ultrasonography (EBUS) also have a role in the staging of lung cancer but, unlike PET/CT, they fail to provide functional information, which can provide clinicians with additional prognostic indications regarding survival and allow estimation of relapse risk based on assessment of the maximum standardized uptake value (SUVmax). The aim of this study was to extrapolate the combined cut-off SUVmax and size of primary lung lesion and to look for a possible correlation with poor disease-free survival (DFS) in patients with stage I and II NSCLC in two-year follow up.
Materials and methods 49 patients with stage I-II NSCLC were included in this study. Pre-surgical FDG-PET/CT study was performed for all patients. The relationship between SUVmax and two-year DFS was measured. The cut-off value for SUVmax and primary tumor size with the best prognostic significance and probability of two-year disease-free survival (2-year DFS) were calculated. Finally the correlation between the combination of both cut-offs was correlated with the 2-year DFS.
Results 36 patients were disease-free at 24 months (DFS= 73.4%) with an average SUVmax value of 8.96 ± 5.26 and tumor size of 31.27 mm ± 18.65. Thirteen patients had recurrence of disease within 24 months (DFS = 10 months). These patients had average SUVmax = 12.8 ± 5.3 and mean primary lung lesion size = 40.5 mm ± 9.4. The optimal cut-offs to predict DFS were 9.00 for SUVmax (p=0.0013) and 30 mm for tumor size (p=0.0028). Patients with SUVmax>9 and primary lesion size>30 mm had an expected two-year DFS of 37.5%, which raised to 90% if the tumor was<30 mm and/or SUVmax was<9. The prognostic stratification of DFS using combined SUVmax and lesion size cut-offs was slightly more accurate than using lesion size alone (p=0.0003 versus p=0.0028).
Conclusions Our data suggested that lesion size and SUV are independent prognostic factors. In patients with NSCLC stage I-II the combination of a dimensional cut-off (30 mm) with a SUVmax cut-off (9) could identify a subgroup of patients presenting a high risk of recurrence of disease within two years of surgery.

The predictive role of metabolic response following stereotactic body radiotherapy for lung cancer

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Background and aim Stereotactic body radiotherapy (SBRT) has emerged in the last decade as a treatment option for patients with medically inoperable stage I non-small cell lung cancer (NSCLC) and for patients with oligometastic lung tumors. Response assessment after SBRT is typically performed by CT. However, morphological changes such as tumor shrinkage can take several months and treatment-induced lung changes may be sometimes mistaken for tumor recurrence. An accurate and timely response assessment is essential as a salvage therapy, including surgical resection, and may be proposed after SBRT failure. The aim of this study was to assess whether metabolic changes observed on[18]F-FDG PET-CT performed 3 months (post-1 PET-CT) and 12 months (post-2 PET-CT) after the end of SBRT, could predict patients' outcome in medically inoperable early-stage NSCLC and in oligometastatic patients.
Materials and methods Seventeen patients (10 males; mean age 76±7 years; 12 NSCLC and 5 oligometastatic patients) underwent [18]F-FDG PET-CT at baseline (pre-SBRT PET-CT), 3 months (post-1 PET-CT) and 12 months (post-2 PET-CT) after SBRT (dose delivered 50-60Gy in 3-4 fractions). Diagnostic CT scan was performed at 3-month intervals for the first 2 years. Metabolic response was evaluated qualitatively (positive/negative scan) and semi-quantitatively using the following parameters: SUVmax, TBR (tumor-to-background-ratio), MTV (metabolic tumor volume), DSUVmax, DTBR and DMTV (individual variation in SUVmax, TBR and MTV, expressed as a percentage of the baseline value). Metabolic changes were related to local control rate (absence of any increase in lesion size on 2 consecutive CT scans).
Results On pre-SBRT PET-CT all target lesions showed [18]F-FDG uptake. On post-1 PET-CT, 6/17 (35%) target lesions were negative, and remained negative at post-2 PET-CT; 8/17 (47%) were positive (4 became negative and 4 remained positive at post-2 PET-CT); 3/17 (18%) scans were not evaluable due to concomitant radiological signs of acute inflammation (1 persisted as positive at post-2 PET-CT while the other 2 became negative). At a median follow-up of 41 months (range: 17-71 months), none of the patients with a negative post-1 scan (n=6) had local failure; 4/8 (50%) patients with positive post-1 PET-CT became negative on following scans and none of them had local failure; 2/4 (50%) patients with both positive post-1 and post-2 PET-CT had local recurrence, while the other 2 patients showed local control; 2/3 patients with non-evaluable post-1 PET-CT had local failure while the remaining patient had a negative following scan and no local recurrence. The univariate analysis showed that MTV, ΔMTV and ΔTBR measured on post-1 PET-CT can predict local failure (p=0.031) and all metabolic parameters evaluated on post-2 PET-CT (p=0.013). On multivariate analysis, only ΔTBR between post-2 and pre-SBRT PET-CT was significantly lower (p<0.001) in patients with local failure than in patients with local control. A percentage reduction less than 37% of this parameter provided the best diagnostic performance with a sensitivity of 100% (CI = 40-100) and specificity of 85% (CI = 55-98).
Conclusions The results of this pilot experience suggest that a negative [18]F-FDG PET-CT scan performed 3 months after the end of SBRT can predict local controlas well as a >37% reduction of DTBR between baseline and 12-month PET-CT. On the other hand, the presence of[18]F-FDG uptake or concomitant acute radiation pneumonitis 3 months after SBRT needs further monitoring or biopsy before a therapeutic decision.

[68]Ga-peptide PET/CT and peptide radioreceptor therapy in small-cell lung cancer: our experience in patients in the extensive disease stage

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Background Small-cell lung cancer (SCLC) accounts for 15–18% of all lung cancer. The prognosis in the extensive disease (ED) stage is poor (median survival=10 months, 2-year survival rate=10%) and ef-

fective treatments are still lacking. The presence of somatostatin receptors (SSTR-2) in 80-100% of SCLC cells, together with promising results of peptide radioreceptor therapy (PRRT), prompted us to test PRRT in this clinical setting. We used ^{68}Ga-peptide PET/CT in ED-SCLC to determine SSTR expression and identify patients suitable for PRRT. In treated patients, we also evaluated PRRT efficacy.

Patients and methods From 2008 to 2011, ^{68}Ga-peptide PET/CT was performed in 24 ED-SCLC patients (M/W=23/1; mean/median age=63.5/62.5 years, range=41-79) to evaluate SSTR expression. ^{68}Ga-peptide PET/CT was compared to CT scan (gold standard). Images were analyzed using a score from 0 to 3+ (liver uptake=reference organ). Patients were considered eligible for PRRT in the presence of an uptake score of 3+ in the majority of lesions. Dosimetry was performed in all treated patients. Mean activity/cycle of 3.1 GBq (^{90}Y-PRRT) or 5.3 GBq (^{177}Lu-PRRT) was injected. PRRT efficacy was assessed clinically and using the RECIST criteria.

Results ^{68}Ga-peptide PET/CT scans were positive in 20/24 (83%) patients; the concordance rate with CT scans was 37.5% (9/24). On the basis of radiopharmaceutical uptake, the patients were scored as follows: 1+, 2+ and 3+ in 7/24, 1/24 and 12/24 cases, respectively. The primary tumor showed uptake in 16/24 cases (1+=8/24; 2+= 1/24; 3+=7/24). Metastasis in the adrenals was identified in all cases (3+=4/4). Metastases in the brain, bone, liver and lymph nodes showed ^{68}Ga-peptide uptake in 2/5 (all 1+), 12/16 (1+=2/16; 2+= 1/16; 3+=9/16), 3/8 (3+=3/8) and 17/20 cases (1+=7/20; 2+= 1/20; 3+=9/20), respectively. Among the 12 patients selected for PRRT one was not treated due to failure to meet other inclusion criteria. Dosimetric estimates showed a mean adsorbed dose of 7.5 Gy (range 4-21) for the kidney BED and 0.43 Gy (range 0.1-1.7) for the bone marrow. No toxicities were recorded after injection of the radiopharmaceutical for the dosimetric studies. Of the 11 treated patients, seven received a single PRRT administration; three received 2 PRRT cycles, and one patient received 3 PRRT cycles. Repeated cycle administrations were performed 76 ± 17 days apart (range 50-89). In all cases, post-therapeutic scintigraphy showed adequate radiopharmaceutical distribution. Hematological toxicity, including anemia (grade 2) and thrombocytopenia (grade 2-3), occurred in 3/11 patients (27%). One patient with multiple liver metastases presented raised bilirubin levels (grade 3) after the second PRRT cycle, considered to be disease-related. A transient mild increase in the creatinine level (grade 1) was observed in one case after ^{90}Y-PRRT. A worsening of clinical conditions was observed in all the patients and PD for the appearance of new tumor lesions, confirmed by CT scan, was determined. Disease progression occurred 48 days (mean, range 7-92) after PRRT.

Conclusions In our series the use of radiolabeled SST-analogs gave encouraging findings in the diagnostic workup of ED-SCLC since ^{68}Ga-peptide PET/CT was positive in 83% of ED-SCLC patients. Enhanced SSTR expression was found in 50% of cases. PRRT was ineffective in all patients. PRRT-related toxicity occurred in 3/11 patients. Hopefully success of targeted therapies in ED-SCLC should be applied using an appropriate timing in combination with other treatments.

Diagnostic performance of dual-tracer PET/CT in staging well-differentiated neuroendocrine tumors of the lung

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Background Different PET tracers may be useful in staging lung neuroendocrine tumors (LNETs). The aim of this study was (a) to calculate the diagnostic accuracy of PET/CT using two different tracers (^{18}F-FDG, used to study glucose metabolism, and ^{68}Ga-DOTANOC, used to study somatostatin receptor expression) in a series of patients with suspected LNETs and (b) to correlate histology with PET findings to assess which is the best PET tracer for staging well-differentiated LNETs.

Methods Thirty-one patients (14 males/17 females; mean age: 63 years) with suspicion of LNETs based on radiological and/or biochemical findings underwent PET/CT with ^{18}F-FDG and ^{68}Ga-DOTANOC for presurgical staging. Detection rates of LNETs on a per patient-based analysis were calculated. Histology was used as reference standard. Patients evaluated for restaging were excluded from the analysis. An exact Fisher's test was used to correlate histology and PET findings.

Results Pathology showed 14 typical carcinoids, 11 atypical carcinoids and six benign pulmonary lesions. ^{18}F-FDG-PET/CT was true positive for LNET in 13 cases, true negative in six and false negative in 12. ^{68}Ga-DOTANOC-PET/CT was true positive for LNET in 19 cases, true negative in six and false negative in six. No false positive results were found using either method. Overall detection rates of ^{18}F-FDG-PET/CT and ^{68}Ga-DOTANOC-PET/CT were 52% (95% confidence interval - 95%CI - : 31-72) and 76% (95%CI: 55-91), respectively.

With regard to typical carcinoids, ^{18}F-FDG-PET/CT and ^{68}Ga-DOTANOC-PET/CT showed detection rates of 21% (95%CI: 5-51) and 93% (95%CI: 66-100), respectively ($p<0.05$). For atypical carcinoids, the detection rates of ^{18}F-FDG-PET/CT and ^{68}Ga-DOTANOC-PET/CT were 91% (95%CI: 59-100) and 55% (95%CI: 23-83), respectively. Discordant findings using both PET tracers were found in 58% of cases and in 72% of well-differentiated LNETs. Combining both PET methods, the detection rate for LNETs was 100%. A significant association between histological type and dual-tracer PET/CT findings was found ($p<0.05$).

Conclusions Overall the diagnostic performance of ^{68}Ga-DOTANOC-PET/CT is superior to that of ^{18}F-FDG-PET/CT in staging well-differentiated LNETs, particularly in typical carcinoids. Nevertheless, ^{18}F-FDG-PET/CT seems to be more useful than ^{68}Ga-DOTANOC-PET/CT in detecting atypical carcinoids. Both PET/CT methods could be performed when the LNET histological subtype is unknown.

ONCOLOGY 3 – BREAST

Preoperative identification of residual breast tumor following neoadjuvant therapy: a breast-specific γ-camera (BSGC) planar scintigraphy and SPECT/CT comparative study

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Aim Clinical examination and conventional imaging procedures, such as mammography and breast ultrasound, have proved to be of limited value both in assessing complete remission and in estimating the extent of residual disease in patients with locally advanced primary breast cancer (BC) following neoadjuvant therapy. Conventional planar scintimammography has also proved to be unsuitable for the identification of small-size tumoral residues. Both breast-specific γ-camera (BSGC) scintigraphy and SPECT/CT are emerging as useful diagnostic tools in the detection of primary BC. In the present study we compared these two radioisotopic procedures in the preoperative identification of residual disease in BC patients following neoadjuvant therapy.

Methods Thirty-nine consecutive female patients (age: 26-82 yrs) with biopsy-proven primary BC (35 invasive ductal, 3 invasive lobular and 1 invasive mucinous) scheduled for surgery following neoadjuvant chemo- (31 cases) or hormone (8 cases) therapy were studied. Starting 10 min. after the i. v. injection of ^{99m}Tc-tetrofosmin (740 MBq), all patients underwent breast scintigraphy in both cranio-caudal and medio-lateral oblique views (600 sec./view) using a high-resolution BSGC (LumaGEM 3200S/12k, Gamma Medica Ideas Inc.). A SPECT/CT study was then acquired, including both breasts in the field of view, using a dual-head gamma camera integrated with an x-ray tube for low-dose CT (Infinia Hawkeye 4, GE Medical System). SPECT images were corrected for attenuation and scattering, reconstructed by the iterative method (OSEM) and fused with CT images using a dedicated package (Xeleris Workstation, GE Medical System). Scintigraphic data were correlated with surgical histopathological findings in all cases.
Results 7/39 patients (18%) had a complete remission following neoadjuvant therapy, without any evidence of residual disease at surgery, while 32/39 patients (82%) had tumor residues that were macroscopic in 28/32 cases and microscopic in the remaining 4/32 cases. Both BSGC scintigraphy and SPECT/CT were true negative in the 7 patients without residual disease (specificity: 100%), while BSGC scintigraphy detected residual tumors in 31/32 cases and SPECT/CT in 28/32 (sensitivity: 97 and 87.5%, respectively; $p>0.05$). Both procedures also gave a precise definition of breast quadrant localization in all positive cases. BSGC scintigraphy was false negative, concordantly with SPECT/CT, in one patient who had microscopic tumor foci scattered in a fibrotic area. Only SPECT/CT was false negative in 3 further patients, one of whom presented a microscopic invasive ductal carcinoma and 2 had macroscopic invasive tumors (a mucinous carcinoma and a lobular carcinoma, respectively). The diagnostic accuracy values were 97.4% for BSGC scintigraphy and 89.7% for SPECT/CT.
Conclusions In the present study, both BSGC scintigraphy and SPECT/CT proved to be highly accurate diagnostic tools in the preoperative identification of residual BC following neoadjuvant therapy. However, BSGC scintigraphy proved to be more sensitive than SPECT/CT and should thus be preferred. However, SPECT/CT could represent an useful alternative when high-resolution dedicated breast devices are not available.

Single-nucleotide polymorphisms and FDG-PET in breast cancer

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Background and aim Breast cancer (BC) is the leading cause of cancer-related death in women worldwide and presents distinct subtypes associated with different clinical outcomes. Understanding this heterogeneity represents a key factor for the development of targeted preventive and therapeutic interventions. Positron emission tomography (PET) with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) has been widely shown to be a clinical imaging modality suitable for BC detection and staging in which the glucose analog supplies metabolic information about the tumor. The completion of nine large genome-wide association studies introduced single-nucleotide polymorphisms (SNPs) as risk factors for BC. Although the possible correlations between gene polymorphisms and FDG uptake is considered an innovative and interesting example of the translational medicine approach, wherein information from multiple sources is combined with the aim of providing more personalized care, the number of scientific papers is still limited. The candidate targets currently used for these studies are polymorphisms in the Glucose Transporter 1 gene and hypoxia-related genes. We investigated the possible association of SNPs in the GLUT1, HIF-1a, EPAS1, APEX1, VEGFA and MTHFR genes with FDG uptake in BC patients.
Methods In 26 Caucasian individuals with primary BC, whole-body PET-CT scans were obtained and quantitative analysis was performed by calculating the maximum standardized uptake value normalized to body-weight (SUVmax) and the mean SUV normalized to body-weight corrected for the partial volume effect (SUVpvc). The Human Gene Mutation Database and dbSNP Short Genetic Variations database were used to analyze gene regions containing the selected SNPs. Genomic DNA was extracted from peripheral blood using the QIAamp DNA blood mini kit (Qiagen). BC genotyping was performed by means of sequencing analysis using a 3500-Dx Genetic Analyzer (Applied Biosystems).
Results A limited number of studies, sometimes controversial, describe possible associations between FDG uptake and SNPs. For this reason, this field needs to be further explored and clarified. None of the potentially useful polymorphisms selected and previously suggested were statistically associated with tracer uptake (using both SUVmax and SUVpvc).
Conclusions The possible functional influence of specific SNPs on FDG uptake needs further studies in human cancer diseases. In summary, this is, to our knowledge, the first study to investigate the association between a large panel of SNPs and FDG uptake specifically in BC patients. This work provides an example of the multidisciplinary and translational medicine approach applied to the study of BC, in which the possible correlation between gene polymorphisms and tracer uptake may be considered to improve personalized cancer treatment and care.

^{18}F-FDG PET as a tool for imaging proliferation in breast cancer: correlation between partial volume-corrected SUV and MIB-1 proliferation index

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Aim To assess the role of ^{18}F-FDG quantification with partial volume correction (PVC) as a potential marker of the MIB-1 proliferation index in breast cancer.
Materials and methods Forty breast cancer patients were enrolled in a personalized and integrated protocol demanding close collaboration between the senology, nuclear medicine and pathology departments of the San Raffaele Hospital, Milan, Italy. Patient enrolment was performed by senologists, selecting adult females with breast tumor mass > 1 cm submitted to mammography and with a biopsy-confirmed breast cancer diagnosis, designated for surgical intervention without any pre-surgical treatment. Patients underwent a ^{18}F-FDG PET/CT study before surgery. Patient weight, injected and residual dose were measured in order to provide accurate ^{18}F-FDG PET quantification using the partial volume corrected body-weight standardized uptake value

(PVC-SUV_{BW}). Surgical intervention allowed extraction of the tumor mass and collection of biological samples to be sent to the pathology unit. Excised tissues were sectioned and classified according to the WHO guidelines, allowing measurement of the MIB-1 proliferation index. Measured by the pathologist, the MIB-1 index is intrinsically an ordinal numerical continuous datum, ranging from 0% to 100%, however in our statistical analysis, it was also considered a nominal dichotomous datum; we applied a threshold of 18% for positive staining, on the basis of the mean values obtained from the histopathology lab. The Mann-Whitney test was used to evaluate the differences in PVC-SUV_{BW} between the group showing positive staining of MIB-1 and the group showing negative staining. Univariate linear regression was also applied to evaluate a possible linear relationship between Mib-1 proliferation index and PVC-SUV_{BW}.
Results Using a threshold of 18% for the MIB-1 proliferation index, PVC-SUV_{BW} was found to show significant correlation with MIB-1 proliferation index ($p < 0.05$). In particular PVC-SUV = 4.52 ± 2.92 for tumor with an expression of MIB-1 ≤ 18% and PVC-SUV_{BW} = 9.30±7.40 g/cc for tumor with an expression of MIB-1 > 18%. Univariate linear regression confirmed the relationship between MIB-1 proliferation index and the in vivo PVC-SUV_{BW} biomarker; in fact, higher significance was found for the estimated coefficient of MIB-1 proliferation index ($p<0.001$). Despite this, the significance of the regression was low (R-square <0.3), showing that the linear relationship is not effective to describe mathematically the link between the two variables. An analysis of ROC curves was performed on the two clusters of data. It was established that a value of 4.06 g/cc for PVC-SUV_{BW} can distinguish positive or negative MIB-1 proliferation index values, with a specificity of 70.6% and a sensitivity of 65.0%.
Conclusions A strong correlation between SUV_{BW} and MIB-1 proliferation index was found, suggesting that SUV_{BW} could be considered a possible surrogate marker of proliferation.

Correlation between Standardized Uptake Value of ^{18}F-FDG PET and hormone receptor status, HER2 status, and Ki-67 proliferation index in patients with invasive ductal carcinoma of the breast

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Aim The correlation between the ^{18}F-FDG maximum standardized uptake value (SUVmax) and hormone receptor status remains controversial, possibly due to patient selection bias. The expression of specific molecular markers in invasive ductal carcinoma (IDC) of the breast, such as estrogen receptor (ER), progesterone receptor (PR), HER2 status, and the Ki-67 proliferation index, has direct prognostic and therapeutic implications in the management of these patients. The aim of this study was to correlate tumor glucose use with ER, PR, and HER2 status and Ki-67 proliferation index in breast cancer patients (pts) with IDC. Tumor glucose use was quantified by the ^{18}F-FDG SUVmax.
Methods Breast tumors from 29 consecutive pts with IDC who had undergone ^{18}F-FDG PET prior to surgery were excised and examined for ER, PR, HER2 and Ki67. The association between SUVmax and ER, PR and HER2 status as well as Ki-67 was investigated.
Results There was a significant difference in SUVmax between pts with ER- (n=10) and ER+ (n=19) status, regardless of PR and HER2 status (SUVmax=9.6±3.9 vs 5.8±2.4, P= 0.001). Moreover, there emerged an inverse correlation between the %ER+ cells and SUVmax (r=-0.48, p=0.008). In the ER+ group, there was no significant difference between pts with PR+ and PR- status (p=0.41), and no correlation was found between the %PR+ cells and SUVmax (r=0.31, p=0.2). In this group, there was also no significant difference between HER2+ and HER2- pts (p=0.21). As previously reported, pts with triple-negative status (ER-, PR-, HER2-) had a significantly higher SUVmax than those with ER+/PR+/HER2+ or ER+/PR+/HER2- status. The correlation between SUVmax and Ki67 was not significant (r=0.32, p=0.1).
Conclusions ER receptor status is the most important determinant of SUVmax in pts with IDC, being more important than PR or HER2 status or Ki67. These preliminary results support a growing body of evidence that ER+ and ER- breast cancers have distinct disease-specific patterns.

Role of ^{18}F-FDG PET/CT in suspicion of relapse in 237 patients with breast cancer

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Aim Early detection of recurrence in breast cancer is crucial in order to select the most appropriate therapy and it can improve the prognosis and survival. The aim of our study was to evaluate the performance of ^{18}F-FDG PET/CT in the assessment of suspected recurrent breast cancer in patients who presented with elevated serum tumor markers (CA 15-3 and/or CEA) and/or clinical suspicion of relapse with inconclusive conventional imaging.
Methods We retrospectively evaluated 237 whole-body ^{18}F-FDG PET/CT scans performed at our center over a two-year period (Jan 2010-Jan 2012) in women (aged 33-92 years; mean: 64 years) previously operated on for breast cancer and in whom, during follow up, recurrence was suspected on the basis of elevated serum tumor markers and/or who presented a clinical suspicion of relapse with inconclusive conventional imaging. The ^{18}F-FDG PET/CT scan, performed 1 hour after intravenous injection of ^{18}F-FDG (2.2 MBq/kg), consisted of a whole-body acquisition (6-7 bed positions, 3 min per bed) from the mid-thigh to the base of the skull. All scans were analyzed (visually and by SUV analysis) by two experienced nuclear medicine physicians by consensus. Positive scans were classified, on the basis of the site of the pathological uptake, as local relapse, relapse in the ipsilateral axillary lymph nodes, in distant lymph nodes, or in distant organs (bone, brain, adrenals etc.).
Results The overall positive detection rate (PDR) of ^{18}F-FDG PET/CT was 60% (142 positive scans in 237 patients). In 70 patients (30% of the total positive scans) the ^{18}F-FDG PET/CT scan was negative, showing no evidence of disease, while in 25 patients (10%) it was inconclusive and further evaluation was proposed in the final report. In the 142 positive scans the sites of recurrence were: (a)"loco-regional" in 8% (12/142) of the cases (6% in the site of the tumor and 2% in the ipsilateral axillary region); (b) "distant" in 70% (99/142) of the patients (10% in distant lymph nodes, 20% in the bone, 17% in other distant sites, such as the brain or adrenals, while the majority of these patients (52%) presented multiple distant lesions on ^{18}F-FDG PET/CT examination); (c) "both local and distant" in 22% (31/142) of the patients.
Conclusions ^{18}F-FDG PET/CT is an effective whole-body imaging technique which detects the metabolic changes that usually precede structural findings. In our experience, it is an effective technique

for detecting sites of breast cancer recurrence (PDR: 60%), suspected on the basis of elevated levels of tumor markers and/or suggestive clinical findings with inconclusive conventional imaging, and can lead to the most appropriate treatment approach (local or systemic).

ONCOLOGY 4 – PELVIS

[^{11}C]choline PET/CT for the detection of tumor recurrence in prostate cancer patients with PSA<1.5 ng/mL

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Aim Early detection of prostate cancer (PCa) recurrence is important because the effectiveness of salvage therapy in PCa patients is greater in the presence of low prostate-specific antigen (PSA) values. [^{11}C] choline PET/CT offers potential for early restaging of PCa with low PSA, but selection of patients at high risk of positive [^{11}C]choline PET/CT is desirable in order to optimize salvage therapy. The aim of our study was to identify which variables can predict positivity of [^{11}C] choline PET/CT in PCa patients with PSA <1.5 ng/mL.
Materials and methods We retrospectively included 75 PCa patients undergoing [^{11}C]choline PET/CT for restaging of disease, with rising PSA< 1.5 ng/mL after radical prostatectomy who received neither antiandrogen deprivation therapy nor salvage radiotherapy. Binary logistic regression was used to assess predictive factors of positive [^{11}C]choline PET/CT. The variables analyzed were age, trigger PSA, PSA doubling time (PSADT), pathological stage and Gleason score.
Results Sixteen out of the 75 patients (21%) were positive on [^{11}C] choline PET/CT. Median PSA was 0.61 ng/mL. On univariate analysis, PSADT < 6 months was the only factor significantly associated with an increased risk of positive [^{11}C]choline PET/CT (OR= 7.77, 95% CI: 2.34-25.80; p=0.001). In patients with PSADT < 6 months, the positive detection rate of [^{11}C]choline PET/CT increased to 50%.
Conclusions In PCa patients with biochemical failure after radical prostatectomy and PSA < 1.5 ng/mL, PSADT < 6 months predicts positive [^{11}C]choline PET/CT scan. In patients with PSA < 1.5 ng/mL and PSADT < 6 months, [^{11}C]choline PET/CT may increase by 50% the number of patients in whom salvage therapy is initiated with knowledge of the disease location and the treatment is properly tailored.

Influence of choline PET/CT-guided treatment planning in prostate cancer patients eligible for radiotherapy

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Background and aim [^{11}C-choline PET/CT (Cho-PET) is a valuable imaging modality for the assessment of prostate cancer (PC) patients, mainly indicated for disease restaging in cases of biochemical relapse. So far, very limited evidence concerns its use in image-guided treatment planning of those patients who result eligible for radiotherapy (RT), either at initial diagnosis or in case of salvage/adjuvant treatment. The aim of our study was to analyze the role of Cho-PET in the management of PC patients in this clinical setting.
Materials and methods Between 2007 and 2010, a total of 305 consecutive Cho-PET scans were performed in two different institutions (ICH and IEO, Milan). Among 240 PC patients, who had received no previous RT, we retrospectively analyzed data from 82 Cho-PET scans (74 patients: median age 67.7 years; range 50-83), who were referred to IEO for RT planning at initial diagnosis (9 patients) or in case of biochemical relapse after previous treatment (26 surgery; 39 surgery ± systemic regimen). Median PSA level at Cho-PET (trigger PSA) was 1.6 ng/mL (range 0.1-150 mg/mL). In 23 cases, PET was performed during androgen deprivation therapy. All Cho-PET scans were reviewed and the outcome was classified as positive in the prostate/prostatic bed (T), pelvic lymph nodes (N), distant metastases (M), or as negative (neg). Reference standard for imaging findings was based on a multidisciplinary work-up, including other diagnostic techniques, clinical data and/or follow-up.
Results Of the 82 scans examined, Cho-PET was positive in 45 cases (55%): 22 T (49%), 4 N (9%), and 19 M in combination with T and/or N (42%). The median trigger PSA in T-positive and N/M-positive cases was 7.4 ng/mL (range 2.7-150) and 13.7 ng/mL (range 5.3-139), respectively. On the basis of Cho-PET findings, 28 cases patients proceeded with RT±systemic therapy, whereas in the remaining 17 cases (48%) the therapeutic approach changed. Six patients underwent surgery±RT, 4 received systemic therapy only, and 7 received other treatment. Considering all scans, Cho-PET led to a change in treatment planning in 17/82 (21%).
Conclusions Cho-PET-driven treatment planning seems to be useful in defining the extent of disease and choosing the most appropriate therapy for PC patients. The method results capable of influencing more than 1/5 of all patients' treatment and almost half of those with a positive Cho-PET result.

^{18}F-FDG PET/CT in staging of advanced epithelial ovarian cancer (aEOC): evaluation of the prognostic value of stage III to IV migration

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Background and aim The introduction of ^{18}F-FDG PET/CT in the preoperative management of advanced epithelial ovarian cancer (aEOC) has increased the detection of extra-abdominal metastases, leading to the migration of apparent stage III disease to stage IV. The aim of this retrospective study was to evaluate the prognostic impact of stage migration in these patients.
Patients and methods Patients with suspected pelvic mass underwent ^{18}F-FDG PET/CT within two weeks prior to standard debulking surgery. Survival rates of patients with clinical stage III and PET/CT stage

IV disease were compared using Kaplan Meier curves.
Results Ninety-seven patients with histologically confirmed aEOC were considered in this analysis. 79 patients were diagnosed with FIGO stage III, and the remaining 18 patients with stage IV. On the basis of the results of PET/CT, 59 patients were classified as affected by stage III disease and 38 as stage IV. Therefore, stage migration involved 20 patients. Median age was similar in the PET/CT stage III and IV groups (58 and 59 years, respectively), preoperative CA125 levels were 1597 and 2273 UI/ml. In both groups the majority of patients had a serous histotype (63 and 61%). All the patients underwent debulking surgery and adjuvant platinum-based chemotherapy. A residual tumor <1 cm was achieved in a significantly higher proportion of patients with PET/CT stage III than IV (32/59, 54% and 6/38, 16% respectively, Fisher's exact test p <0.001). Relapse rate was similar in the two groups (66 and 68%, respectively). Interestingly, 10/20 patients with discordant stage (clinical stage III-PET/CT stage IV) experienced a supradiaphragmatic recurrence. The survival analysis for patients with clinical stage III and IV showed a similar progression-free survival (PFS) (17 and 15 months, p: 0.24, HR: 0.65, 95% CI 0.32 to 1.33) and overall survival (OS) (45 and 42 months, p: 0.94, HR: 1.04, 95% CI 0.40 to 2.68). Comparing patients with PET/CT stage III and IV, PFS was 16 and 17 months (p: 0.81, HR: 1.06, 95% CI 0.63 to 1.79) and OS 39 and 51 months (p: 0.93, HR: 1.03, 95% CI 0.50 to 2.09), respectively. Finally, comparing patients with clinical-PET/CT stage III, clinical stage III-PET/CT stage IV, and clinical-PET/CT stage IV disease, PFS was 17, 17 and 12 months (p: 0.34) respectively, and OS was 51, 41 and 35 months (p: 0.72).
Conclusions ^{18}F-FDG PET/CT is able to identify patients with subclinical extra-abdominal localization of aEOC. Since these patients show an intermediate OS compared to clinical stage III and IV aEOC, the presence of distant metastasis could be regarded as the expression of a higher aggressiveness of the tumor, as suggested both by the lower proportion of stage IV patients with residual tumor <1 cm and by the oncological outcome. Hence, in these patients, the maximum surgical and chemotherapeutic effort should be made.

Impact of PET-CT in staging and defining treatment volumes in gynecological cancer. The experience of two radiotherapy departments (Mauriziano Hospital in Turin and IRCC in Candiolo)

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Aim The definitive treatment and prognosis in gynecological cancer is markedly affected by the extent of disease at the time of diagnosis. MRI/CT studies have been widely used in staging gynecological cancers, however they have shown suboptimal accuracy. Many studies have confirmed that FDG-PET detects abnormal LN regions more often than do CT/MRI studies and that PET is a better predictor of survival in patients with gynecological cancer. The aim of our study was to evaluate the impact of FDG-PET in gynecological cancer staging, definition of treatment volumes, and reduction of inter-observer variability in contouring.
Materials and methods Between January 2008 and August 2012, 136 patients with histologically confirmed gynecological cancer, candidates for radiotherapy (adjuvant, radical or palliative), were referred to the radiotherapy units of the Mauriziano Hospital and IRCC; 59 of these patients underwent a PET-CT scan before the definition of a treatment program. Of these 59 patients, 51 had cervical, 7 endometrial and 1 vaginal carcinoma; 10 underwent adjuvant radiotherapy after radical surgery (RT 50 Gy, HDR boost 10 Gy/2 fr), 8 palliative RT (dose 50-60 Gy), and 41 radical chemoradiotherapy (RT dose 64-67 Gy, boost HDR 21 Gy/3 fr or 24 Gy/4 fr). Thirty-five patients were treated with 3D conformal radiotherapy, 24 with the IMRT sib technique. Treatment planning was performed according to the fusion between PET & simulation CT; the GTV was defined using a semi-quantitative method (cut-off value 2.5 SUV) in order to reduce inter-observer variability.
Results Staging was modified by PET in 8 patients (13.5%): PET-CT revealed distant metastasis and changed the treatment plan (patients underwent chemotherapy or palliative RT). In 29 patients (49.1%) staging was confirmed on PET-CT, MRI and CT imaging and no change was made to the therapeutic decisions, contouring and dose prescription. In the remaining 22 patients (37.4%) the disease was upstaged: PET-CT showed abnormal LF in the pelvis or lomboaortic chains, not previously revealed by MRI and CT. PET-CT could identify nodal metastases even in nodes showing normal dimensions on CT/MRI. In these patients contouring was more precise thanks to PET-CT simulation fusion and we were able to administer higher doses to PET-positive areas. In the postoperative radiotherapy group, PET revealed pelvic nodal metastasis in only 1 patient.
Conclusions Our work confirmed the findings regarding the clinical impact of PET-CT imaging in RT published in other papers. Correct selection of patients for different treatment options, accurate definition of target volumes and accurate contouring allowed us to increase the dose delivered to the tumor and, at the same time, to reduce toxicity. This procedure also improved accuracy in contouring and delivering higher doses to GTV PET, particularly in the IMRT group. Further studies are needed to evaluate problems related to PET response evaluation and prognostic information.

The role of "early" and/or "late" ^{18}F-FDG PET-CT in the prediction of histopathological outcome in patients with locally advanced cervical cancer treated with neoadjuvant chemoradiotherapy followed by radical surgery

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Aim To prospectively evaluate the predictive value of "early" and "late" fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) in patients with locally advanced cervical cancer (LACC) treated with neoadjuvant chemoradiation followed by radical surgery.
Materials and methods From September 2010 to September 2012, 40 patients (mean age 50.2 ± 11.7 years) completed the therapeutic protocol and were included in the analysis. All patients underwent ^{18}F-FDG PET-CT at baseline (''staging'' PET-CT), after 2 weeks of treatment (''early'' PET-CT) and 6-8 weeks after the end of treatment (''late'' PET-CT). Post-surgical histological examination was used as refer-

ence standard. PET-CT images were evaluated qualitatively and semi-quantitatively by calculating the maximum standardized uptake value (SUVmax). The parameters measured were: SUVmax of the primary tumor (T) on "staging", "early" and "late" PET-CT and individual variations in SUVmax (ΔSUV), expressed as a percentage of the baseline value. Lymph nodes (N) were evaluated only qualitatively. Receiver operating characteristic analysis was performed using "early" and "late" ΔSUV. The area under curve (AUC) was calculated to assess the accuracy of ΔSUV in predicting histological response; if the test was judged at least moderately accurate (AUC >0.7) a cut-off maximizing sensitivity and specificity was chosen.
Results On histopathological examination of the primary tumor, 22/40 patients (55%) showed no residual disease, 14/40 patients (35%) microscopic residual disease, and 4/40 patients (10%) macroscopic residual disease. The mean T SUVmax was 13.0±4 at "staging", 7.4±3.8 at "early" and 2.4±1.1 at "late" PET-CT; the mean values of "early" and "late" ΔSUV were 41.8±26.1% and 79.4±12.1%, respectively. AUC was 0.72 (95% confidence interval 0.56-0.88) for "early" ΔSUV and 0.77 (95% confidence interval 0.61-0.92) for "late" ΔSUV; indeed, both "early" and "late" ΔSUV were considered accurate enough in predicting the outcome. An "early" ΔSUV ≥46% demonstrated 88.9% sensitivity and 63.6% specificity in predicting a complete histopathological response; a "late" ΔSUV ≥82.9% demonstrated 83.3% sensitivity and 59.1% specificity in predicting a complete histopathological response. FDG uptake in pelvic N was visually detectable in 16 patients on "staging" PET-CT, in 12 on "early" PET-CT, and in 3 on "late" PET-CT.
Conclusions In patients with LACC, "early" and "late" PET-CT seem to be useful in monitoring the metabolic changes induced by therapy. Individual variation of ΔSUV is the parameter found to best evaluate metabolic changes; it allows to predict histopathological outcome with a possible impact on treatment planning. "Early" PET-CT is a promising tool for distinguishing patients who respond to treatment from those who do not, in order to plan a more conservative approach in responsive patients and intensify radio-chemotherapy or switch to alternative treatment strategies in non-responsive ones.

ONCOLOGY 5 – HAEMATOLOGY

PET/MRI compared to PET/CT in malignant lymphoma: initial experience

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Background Hodgkin and Non-Hodgkin lymphomas (HLs and NHLs) are the fifth most frequently occurring type of cancer in the western world. Combined positron emission tomography and computed tomography (PET/CT) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is an invaluable tool for staging lymphoma patients, predicting therapy outcomes and restaging after therapy. PET/MRI is a new, integrated diagnostic imaging modality which allows for both functional molecular imaging and high-resolution soft tissue imaging, limiting radiation exposure to the radiation dose from ^{18}F-FDG alone.
Objective To compare PET/MR to PET/CT regarding their ability to assess lymphomatous lesions.
Materials and methods We retrospectively evaluated 10 patients with malignant lymphoma who first underwent FDG-PET/CT (Philips Gemini TF PET/CT, Philips Healthcare, Andover, MA) followed by a PET/MRI (Philips Ingenuity TF PET/MRI, Philips Healthcare, Andover, MA) without an additional FDG injection. The PET/MRI consists of a time-of-flight PET combined with a high-field 3.0T MRI system. For MRI-derived attenuation correction, a 3D T1-weighted spoiled gradient echo sequence (TE 2.3 ms, TR 4 ms, 2 degree flip angle) was acquired. All scans were evaluated independently by two physicians. Equal weighted kappa (k) was applied to the number of the detected lesions identified as lymphomatous infiltrations. Intra-reader agreement between PET/CT and PET/MRI and inter-reader agreement regarding PET/MRI findings were calculated. Lesion localization assessment comparing PET/MRI to PET/CT was also performed.
Results Intra-reader agreement regarding the number of detected lymphomatous lesions on PET/CT and PET/MRI was excellent for both readers ($k_1 = 0.84$, $k_2 = 0.86$). Inter-reader agreement regarding the number of detected pathologic lymphomatous lesions on PET/MRI was good (k=0.4). Reader 1 rated more lesions on PET/MRI as pathologic, while Reader 2 rated those as "suspicious". Lesions localization was congruent between corresponding PET/MRI and PET/CT for Reader 2, identifying the same stage of the disease according to the Ann-Arbor classification. Reader 1 detected one bone lesion on PET/MRI, not visible on PET/CT, that would change the stage of the disease.
Conclusions PET/MRI compared to PET/CT shows promising initial results in evaluating lymphoma patients. MRI offers the addition of specific sequences and techniques, such as diffusion weighted imaging (DWI), which could improve the diagnostic accuracy. Furthermore, PET/MRI has a lower radiation exposure which is particularly important for sequential treatment monitoring and surveillance as well as in pediatric patients.

^{18}F-FDG PET/CT evaluation of response to chemoimmunotherapy of primary mediastinal large B-cell lymphoma (PMLBCL): comparison of the performance of different reporting criteria

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Background Primary mediastinal large B-cell lymphoma (PMLBCL) is an uncommon variant of diffuse large B-cell lymphoma arising from thymic cells. It is aggressive with an unfavorable prognosis, CD20 positive, with tendency to recur in the primary site of origin, typically presenting with a large mediastinal mass and often with superior vena cava obstruction symptoms. The persistence at the end of chemotherapy of residual uptake at the site of previous PMLBCL can difficult to interpret. The aim of this study was to compare different evaluation criteria (International Harmonization Project – IHP, Deauville 5-point scale and ΔSUV) in this setting.
Materials and methods Twenty-four patients with PMLBCL (9 M, 15 F; mean age 37.17±11.98 yrs), all treated with R-CHOP or R-CHOP-like regimens and radiotherapy, who had undergone baseline ^{18}F-FDG PET/CT (b-PET) and end-of-chemotherapy ^{18}F-FDG PET/CT (f-PET) scans at our institution between July 2004 and January 2012, were retrospectively re-evaluated; the mean clinical follow-up period was 37.21±18.26 months, at the end of which 3/24 (12.5%) were in PD, 21/24 (87.5%) in CR. Outcome at clinical follow-up was taken as gold standard. SUVmax of the bulky mass at staging and of the residual mass on CT after chemotherapy, and SUVmax of the liver and of the mediastinal blood pool were calculated for all patients. All f-PET scans were evaluated dichotomously by means of IHP criteria and of the 5-point scale, using score 3 as threshold; f-PET vs b-PET ΔSUVs

were calculated as a percentage value considering two threshold criteria: 66% and 77% decrease.
Results IHP criteria analysis: 23 patients were positive, 1 was negative. Sensitivity (SE): 100%; specificity (SP): 4.76%; positive predictive value (PPV): 13%. 5-point scale criteria analysis (scores 1, 2 and 3 considered negative): 16 patients were positive, 8 negative. SE: 100%; SP: 38%; PPV: 18.75%. ΔSUV analysis with 77% decrease: 8 patients were positive (ΔSUV≤77%), 16 negative (ΔSUV> 77%). SE: 100%; SP: 76%; PPV: 37.5%. ΔSUV analysis with 66% decrease: 4 patients were positive (ΔSUV≤66%), 20 negative (ΔSUV > 66%). SE: 100%; SP: 95.24%; PPV: 75%: all three patients in PD were correctly identified by this criterion; the fourth was positive for all criteria after chemoimmunotherapy but is in persistent CR after radiotherapy.
Conclusions In our population (homogeneous but small, retrospective and all consolidated with RT), a percentage reduction of more than 66% appears to strongly predict outcome, better than the other PET criteria for evaluation of response, in possible accordance with the characteristics of this particular pathology.

Is the Deauville 5-point scale a feasible tool for ^{18}F-FDG PET scoring in clinical routine for reassessment of patients with Hodgkin lymphoma?

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Aim The Deauville 5-point scale (5-PS) was first proposed in 2009 as a means to standardize evaluation and to reduce the impact of interobserver variability of ^{18}F-FDG PET performed after two cycles of standard chemotherapy with adriamycin, bleomycin, vinblastine and dacarbazine (i-PET) in clinical trials prospectively testing its predictive value in the early identification of responders from non-responders in Hodgkin lymphoma (HL) patients. We retrospectively compared the results reported by control reviewers and local nuclear medicine physicians (NMPs) with the purpose of investigating whether the 5-PS might be a feasible tool in clinical routine for the evaluation of the i-PET in patients with HL.
Materials and methods From all the patients enrolled between 2009 and 2012 in the Response Adapted Treatment in HL (RATHL) trial, devoted to patients with stage II-IV HL, we selected a cohort of 88 Italian cases evaluated, at 10 referral Italian nuclear medicine centers, on i-PET, which was to be reviewed by the Italian core lab in Modena prior to continued treatment. The i-PET was independently scored at local centers and at the Core lab according to the 5-PS, and was judged "negative" if a score 1 to 3 was assigned, and "positive" if it was scored 4 or 5. While the reviewers at the Core lab were well trained in reporting using the 5-PS, the local NMPs did not receive specific training in its use. The strength of agreement between local NMPs and the Core lab was evaluated by the Landis and Koch-Kappa's Benchmark Scale, according to which Kappa indices ranging from 0.61 to 0.80 correspond to substantial concordance and Kappa indices between 0.81 and 1.00 correspond to almost perfect concordance.
Results Of the 88 i-PETs, agreement between local centers and the Core lab with respect to the 5-PS specific score was obtained in 77.3% of cases, with a Kappa index of 0.66 (95% confidence interval 0.51-0.80). In particular, i-PET score 1 evaluation was centrally confirmed in 38/51 local reports (74.5%), score 2 in 7/8 (87.5%), score 3 in 5/8 (62.5%), score 4 in 10/13 (76.9%), and score 5 in 8/8 (100%). These results showed score 3 to be the most crucial point of the 5-PS; nevertheless, only one patient was reclassified as positive at the Core lab. Overall, 63/67 (94.0%) and 19/21 (90.5%) i-PETs locally reported as negative and positive, respectively, were centrally confirmed (82/88 cases, 93.2%), with a Kappa index of 0.82. The main reasons for lack of consensus were incongruous evaluation of residual uptake of initial bulky masses and of persistent inguinal lymphadenopathy.
Conclusions Our results confirmed almost perfect agreement between local and central reporting of the i-PET as negative or positive according to the 5-PS, suggesting that it could be usefully adopted for clinical practice assessment of i-PET by all nuclear medicine physicians.

Role of interim PET/CT in the clinical management of diffuse large B-cell non-Hodgkin's lymphoma (DLBCL)

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Introduction Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin's lymphoma (NHL), accounting for about 30% of all NHLs. Staging procedures include clinical evaluation, LDH determination and contrast-enhanced computed tomography. [^{18}F]-fluorodeoxyglucose PET/CT, performed at diagnosis as well as during and at the end of treatment, is becoming increasingly important in the workup of these patients. Patients presenting with a disease burden higher than Ann Arbor stage I normally receive rituximab plus cyclophosphamide, doxorubicine, vincristine and prednisone (R-CHOP) every 14 or 21 days for 6 or 8 cycles. Despite the well-known prognostic value of end-of-therapy PET/CT, the role of interim PET/CT in prognostication of this tumor continues to be debated. Evaluation of interim PET/CT during cancer treatment is based on the concept that tumor burden above or below the threshold of detection is linked to treatment failure or success. The aim of this study was to evaluate the role of interim PET/CT in DLBCL, both in early evaluation of response and in predicting clinical outcome.
Methods This multicenter prospective trial comprised a sample of 24 previously untreated patients (median age 60 years), with a disease burden higher than Ann Arbor stage I, all undergoing standard, first-line R-CHOP chemotherapy; all had a complete evaluation including clinical and biochemical evaluation and staging and interim (after two cycles of R-CHOP) and end-of-therapy PET/CT. A qualitative and semi-quantitative analysis using the maximum standardized uptake value (SUVmax) was performed by three independent, expert operators. For analysis of interim PET/CT, a Deauville score of 4 or 5 (uptake equal to or higher than that of the liver) was used as a criterion. At every interim or end-of-therapy scan a PERCIST-based assessment was assigned. A mean follow-up of 12 months was available.
Results 16/24 (66%) patients had interim PET/CT scans showing a complete response (CR) according to PERCIST criteria and were disease-free at follow-up. 8/24 (33%) patients were positive at interim PET/CT, showing either persistent or progressive disease; 2/8 (8%) had a negative end-of-therapy PET/CT and were disease-free at follow-up as well; all patients with persistent disease at interim evaluation showed a Deauville interim score equal to or higher than 4; 6/8 patients showed persistent disease at end-of-therapy PET/CT: two of these six patients underwent additional radiotherapy on sites of active

disease; two showed progressive disease and were offered second-line chemotherapy; one patient died, and one underwent autologous stem cell transplantation.
Discussion Our results confirm that end-of-therapy PET/CT continues to play an important prognostic role in evaluating response to therapy in DLBCL, with NPV and PPV both found to be high; moreover, interim PET/CT shows a high NPV, since 16/18 patients (88%), showing a CR at the end-of-therapy PET/CT, were free of disease at the interim evaluation and 18/18 were disease-free at follow-up. This observation deserves further confirmation, as it could imply changes to interim therapeutic regimens, tailored on a per patient basis. Finally, semi-quantitative analysis obtained by SUV is not superior to a qualitative analysis, and a lesion uptake equal to or greater than liver uptake seems to be reliable for evaluating persistent disease at interim evaluation.
Conclusions Interim PET/CT is an interesting predictive tool in the management of DLBCL and should be further evaluated in order to obtain tailored per patient therapies.

Role of FDG-PET in pediatric HD patients presenting with a partial response on CT

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Background and aim FDG-PET is a mainstay in the assessment of response to treatment of Hodgkin disease (HD) in the adult population, and is becoming a mandatory technique also in the pediatric population. However, the method has not been specifically investigated in children affected by HD and presenting with a partial response (PR) on CT. Thus the aim of this study was to define the role of FDG-PET in this clinical context, considering both interim and end-of-treatment evaluation.
Materials and methods For the study, we analyzed data from 160 HD patients referred to ten different Italian centers to follow the same therapeutic protocol (AIEOP LH2004). Among these, we identified patients showing a PR on CT and studied them with FDG-PET at during treatment (interim) or after completion of therapy. CT findings were classified according to the response, based on the % of volumetric reduction, as follows: Group1, response >75%; Group 2, response >50%, but <75%. Corresponding FDG-PET scans were reported as negative (no evidence of disease/no pathological uptake) or positive for disease. All results were statistically analyzed, using Kaplan-Meier survival curves for progression-free survival (PFS) and Cox proportional hazards regression. Overall, patients were followed up for a mean of 26.5 months and PFS was determined as time from start of treatment to relapse/progression.
Results The assessment, both the interim and the end-treatment evaluation, was not found to be significantly correlated with PFS (p 0.8768 and 0.1141, respectively). Also the Kaplan-Meier analysis with respect to PFS on CT response based on the two-rank classification (grouping) did not differentiate patient outcomes. In this same pool of patients, the interim FDG-PET also failed to show statistical significance (p 0.4727), whereas at the end of treatment FDG-PET data were highly predictive and found to be significantly correlated with PFS (p 0.0028). On univariate analysis, along with the end-treatment PET, age at diagnosis (cut-off 13.3 years) was also found to be predictive (p 0.01681 and 0.03588, respectively), but on multivariate analysis only end-of-treatment PET evaluation emerged as an independent predictive factor (p 0.01147).
Conclusions Response assessment with FDG-PET at the end of treatment in pediatric HD overcomes difficulties deriving from response uncertainty due to PR on CT. These findings however were not confirmed for interim PET, where the method seems to add nothing to the morphological information.

ONCOLOGY 6 – MISCELLANEOUS

Prediction of neoadjuvant chemotherapy response by ^{18}F-FDG PET\CT in bone sarcomas

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Aim Neoadjuvant chemotherapy is fundamental to improve survival in patients with bone sarcomas. A complete or good response to therapy leads to conservative surgery, improving the patient's quality of life, and is a good prognostic factor. The current standard for neoadjuvant chemotherapy response evaluation in bone sarcomas is necrosis on histopathology. However, non-invasive and overall scanning techniques such as FDG PET/CT would be very useful to guide the therapy. The aim of the present work was to study the role of FDG PET/CT in the evaluation of neoadjuvant chemotherapy response in bone sarcomas.
Methods The population of the present study consisted of 16 patients affected by bone sarcomas (8 Ewing; 8 osteo; mean age 21 years). They underwent FDG PET/CT staging, biopsy of the mass, standard neoadjuvant chemotherapy, post-therapy FDG PET/CT and radical surgery. SUVmax in the mass was measured before and after therapy and was compared to the percentage of necrosis on histopathology. Patients with a percentage of necrosis ≥90% were considered good responders. ΔSUVmax was calculated as: (SUVmax pre therapy - SUVmax post therapy) / SUVmax pre therapy.
Results According to the percentage of necrosis, 7 patients were good responders while 9 were poor responders. Mean SUVmax before therapy was 8.3±4.3. No statistically significant difference between osteo and Ewing sarcomas was observed in terms of SUVmax before therapy (p=0.36). After therapy there was a significant decrease in SUVmax (3.6±3.3; p<0.001). ΔSUVmax was significantly correlated with the percentage of necrosis (p<0.001), and there was also a statistically significant correlation between SUVmax post therapy and percentage of necrosis (p=0.016) both for Ewing and osteosarcomas. On the basis of a ROC analysis, a SUVmax post therapy cut-off of 2.7 yielded a

sensitivity and a specificity of 71.4% and 77.8%, while a SUVmax decrease of at least 76% yielded a sensitivity and a specificity of 57.1% and 88.9%.
Conclusions On the basis of the findings of the present study, FDG PET/CT may be a very useful tool to non-invasively identify good responders after neoadjuvant chemotherapy in patients with bone sarcomas. As a consequence, PET results can be taken into account to change patient's management, opting for conservative surgery instead of enlarged resection.

Hepatic lesion enhancement through delayed PET/CT scan acquisitions: an optimizing procedure

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Background In order to improve PET sensitivity for the detection of liver diseases, delayed image acquisition was introduced within traditional imaging protocol schedules. A significant decrease of FDG-uptake in normal liver tissue was observed on PET scans carried out 2h or 3h post-injection, while increased cumulative activity was detected in tumor lesions. This results in enhanced tumor vs background contrast on delayed scans. The aim of this study was to evaluate whether detection of liver pathological uptakes might be improved by acquiring delayed images, using bed-acquisition times equal to or longer than those used in early PET scans.
Materials and methods We analyzed PET/CT scans from 75 patients (41 men; age: 58±14 yrs) who underwent early and delayed acquisitions for suspicion of liver disease. Early and delayed images were acquired 60 min and 3 h after injection, respectively. The delayed images were obtained using the same bed-acquisition time already used in the early scans (3.02±0.26 min) in 35 patients (Group 1) and a different bed-acquisition time (1 min longer) in 40 patients (Group 2). The minimum, maximum and average standardized uptake value (SUV) and the lesion-to-background ratio (L/B ratio) were computed by defining a region of interest on the suspected liver site. The final diagnosis of the lesions was defined by biopsy, by surgical specimen or by conventional imaging.
Results Twenty-seven patients received a diagnosis of pathological liver findings and 48 did not. In particular, 12 of the Group 1 and 15 of Group 2 patients showed evidence of liver disease (34 and 38%, respectively). Early L/B ratios were similar in value in all the patients (healthy patients: 1.44 ± 0.39; non-healthy patients: 1.42 ± 0.34; p= 0.784), while late L/B ratios were higher in the patients with liver disease than in those without liver disease (1.66 ± 0.49 vs 1.44 ± 0.44; p= 0.056). Moreover, in Group 1, the late L/B ratio was significantly higher in the patients affected by liver disease than in the healthy ones (1.71 ± 0.49 vs 1.37± 0.31; p= 0.016), whereas similar values between the same subsets of patients were found in Group 2 (1.62 ± 0.51 vs 1.52 ± 0.53; p=0.546). Similar findings were also found, in the two groups, for the SUV average of the suspected lesion.
Conclusions We proved that delayed PET acquisitions add diagnostic information to an early scan in suspected liver lesions, and may help to improve our understanding of hepatic malignancies. It is of crucial importance to determine the optimal bed-acquisition time for liver scanning in delayed acquisitions to prevent L/B ratios from increasing and introducing a bias in diagnostic results.

Role of ^{11}C-choline PET (CHO-PET) in patients affected by hepatocellular carcinoma: diagnostic performance compared with CT/MRI

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Background and aim Hepatocellular carcinoma (HCC) is one of the most frequent solid tumors occurring worldwide and the principal cause of death in patients affected by cirrhosis. Its diagnosis is usually based on a multidisciplinary work-up, including CT/MRI, but these conventional imaging modalities do not guarantee an adequate evaluation of the extent of the disease, especially in the case of metastases outside the liver. Previous studies have proposed ^{11}C-choline PET/CT (CHO-PET) as a potential diagnostic tool for HCC, having the advantage of being a whole-body modality capable of assessing disease status both in hepatic and extra-hepatic sites. However, no direct comparison with the other conventional imaging modalities has been so far reported. The aim of our study was to assess the diagnostic performance of CHO-PET and compare its findings with CT/MRI, in patients affected by HCC.
Materials and methods We prospectively collected data from 23 consecutive patients (M:F=20:3; mean age 70 years) affected by primary or relapsed HCC: 6 patients were at initial presentation and 17 at restaging after HCC recurrence. Our patients were referred for diagnostic imaging before undergoing surgery, radiotherapy or other systemic treatments. In all cases we performed a whole-body CHO-PET scan and a dedicated CT and/or MRI scan, for a total of 25 paired scans. For each modality, we conducted scan-based and site-based analyses to determine diagnostic accuracy. The reference standard for imaging findings included either histology or a multidisciplinary work-up, including clinical and instrumental follow-up.
Results On scan-based analysis, the different imaging modalities, namely CHO-PET and CT/MRI, demonstrated comparable diagnostic accuracy, 86.4% and 88% respectively. On site-based analysis, we found sensitivity and accuracy values of 67.6% and 65.9% for PET, and 71.7% and 69% for CT/MRI. In both cases, we found no statistically significant difference on T-test. In 7/23 (30.4%) patients, the tumor was extended to either locoregional structures or to distant organs (bone, lung). All extra-hepatic lesions were properly detected by CHO-PET (accuracy 100%), whereas CT/MRI could detect only a part of them (accuracy 58.8%). This lack of accuracy is due only in part to the limited field of view during acquisition. The better disease staging with CHO-PET led to a change in treatment planning in 7 patients (30.4%).
Conclusions Our findings confirmed CHO-PET as a valuable imaging modality for the assessment of patients affected by HCC. It shows a comparable diagnostic accuracy with CT/MRI, with as principal advantage its ability to detect extra-hepatic lesions. The better disease staging led to a treatment modification in almost 1/3 of our patients.

Role of ^{18}F-dihydroxyphenylalanine positron emission tomography in the diagnosis and follow-up of adrenal and extra-adrenal paragangliomas

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Aim To establish the clinical value of PET with ^{18}F-dihydroxyphenylalanine (^{18}F-DOPA PET/CT) in patients with adrenal and extra-adrenal paragangliomas (PGLs).
Methods Nineteen consecutive patients (9 men, 10 women, mean age 45 yrs, range 14-75) with suspected primary or recurrent PGLs were enrolled. In addition to ^{18}F-DOPA PET/CT, the patients underwent

complete diagnostic workup, urinary metanephrines measurement, and magnetic resonance and/or CT imaging (in 14/19 and 7/19 cases, respectively). PET was acquired 60 min after ^{18}F-DOPA administration (3 MBq/kg) using a Discovery ST/8 scanner (GE Healthcare, Milwaukee, USA). Interpretation of PET/CT was based both on visual and on semi-quantitative analysis. For all tumor lesions, maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}) were determined; tumor volume (at 40% of SUV_{max}) was also evaluated on the basis of the ^{18}F-DOPA PET/CT images, and the metabolic burden per lesion was determined by multiplying the tumor volume by the SUV_{mean}. Whole-body metabolic tumor burden (WB-MTB) was then calculated as the sum of metabolic burden of all individual lesions per patient. When clinically indicated, patients underwent surgery, and histological confirmation was obtained in 17/19 cases. Eleven of the 19 patients eventually resulted to be affected by PGLs: 8 had head and neck PGLs (1 with coexistent abdominal PGL), 2 had abdominal para-aortic PGLs, and 1 had bone metastases from a primary adrenal PGL. Of the 8 patients without PGLs, 4 had an atypical adrenal adenoma, 2 had lymph node metastases (from papillary thyroid cancer and from renal cell carcinoma, respectively), 1 had ganglioneuroma, and 1 was a disease-free PGL patient at follow-up (despite suspicion of recurrent PGL). Genetic analysis of known susceptibility genes for PGL (VHL, RET, SDHx, TMEM127) was performed in 10/11 PGL patients.

Results Regarding genetic analysis, 3/10 patients with genetic profile proved to be carriers of the SDHD germline mutation, 1/10 of the SDHB, and 1 of the SDHC mutation. ^{18}F-DOPA PET/CT showed pathological foci of uptake in 10/11 PGL patients, with a total of 14 lesions detected. In particular, the ^{18}F-DOPA scan identified all lesions in the 10 patients with head and neck and in the 4 patients with abdominal extra-adrenal PGLs, while it did not detect multiple metastases in a patient with malignant adrenal PGL. Conversely, no abnormal foci of ^{18}F-DOPA uptake were detected in the patients without proven PGL. No difference between mutated and wild-type patients was observed with regard to detection of PGL lesions. Thus, ^{18}F-DOPA PET/CT sensitivity and specificity were both 100% for head and neck PGL, with 100% positive and negative predictive values and 100% diagnostic accuracy. Instead, ^{18}F-DOPA PET/CT sensitivity was 66% in patients with abdominal PGLs, with 100% specificity, 100% positive predictive value, 87.5% negative predictive, and 90% diagnostic accuracy. No differences were found in the SUV_{max} of PGL lesions in the head and neck or of abdominal extra-adrenal PGLs. In the 11 PGL patients, the WB-MTB values assessed by ^{18}F-DOPA PET/CT were not correlated with urinary metanephrines.

Conclusions Because of its high diagnostic performance, ^{18}F-DOPA PET/CT represents a useful tool for detecting/characterizing PGLs, regardless of the genetic pattern.

Role of ^{18}F-DOPA PET/CT in the evaluation of genetically related paraganglioma syndromes

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Aim Paragangliomas (PGLs) are rare tumors deriving from sympathetic chromaffin tissue in adrenal and extra-adrenal abdominal or thoracic locations or from parasympathetic tissue of the head and neck (HNP). PGLs are characterized by a high frequency of hereditary forms, with a propensity for multifocal disease, and may coexist with other tumor types in multiple neoplasia syndromes. Several susceptibility genes for tumors of the entire paraganglial system have been identified, including succinate dehydrogenase (SDH) B, -C, -D, Von Hipple-Lindau (VHL), neurofibromatosis type 1 (NF1), transmembrane protein 127 (TMEM 127) and MYC associated factor X (MAX). The genetically related PGL syndromes are usually characterized by early-onset, multiple, multifocal and recurrent paragangliomas, often non-secreting. Thus, there is a need for a highly sensitive test able to provide a "whole-body" evaluation in patients with the mutations (whether or not they are symptomatic, or have previously had surgery for PGLs), but unfortunately morphological and traditional scintigraphic imaging show low to moderate sensitivity in detecting the lesions. The aim of our study was to evaluate the accuracy of ^{18}F-DOPA PET/CT in patients with the above-mentioned mutations and to investigate its impact on patient management.

Methods We evaluated 20 patients, 9 males and 11 females, age range 9-65 years (mean: 38.55), positive for gene mutations codifying for the subsequent genetic syndromes: VHL (8 pts); SDHD (5 pts); SDHB (3 pts); SDHC (1 pt); TMEM (1 pt); MAX (1 pt); NF1 (1 pt). Fourteen patients had already undergone surgery for PGL (adrenal and/or extra-adrenal), 5 patients were genetically positive (at diagnosis) with biochemical findings and/or conventional imaging suspicious for paraganglioma, 1 patient was genetically positive (at diagnosis) without biochemical, clinical and/or morphological signs of the disease. Urinary normetanephrine levels were positive in 10 patients and negative in 10. Morphological imaging (CT or MRI) was positive in 10 patients (demonstrating a total of 24 lesions), negative or inconclusive in the other 10. For ^{18}F-DOPA PET/CT, a 2.22 MBq/kg/bw activity was injected 1 hour before whole-body 3D acquisition. Histological and/or cytological findings were taken as the gold standard.

Results On a "per-patient"-based analysis, ^{18}F-DOPA PET/CT was positive in 11/20 patients (positive detection rate: 55%), demonstrating a total of 24 areas consistent with disease localization: 7 in the adrenals, 1 in the liver, 2 in the lungs, 3 in the thorax-abdomen (extra-adrenal), 1 in the prostate, 10 in the head and neck. In 5/11 patients (45% of the positive cases, 25% of the overall population), ^{18}F-DOPA PET/CT showed more lesions than conventional imaging; in particular, in 4 of them (36% of all the positive patients), ^{18}F-DOPA PET/CT showed more lesions than morphological imaging and in 1 patient, completely negative on morphological imaging and without normetanephrine increase, ^{18}F-DOPA showed one prostatic lesion. In these 5 patients, ^{18}F-DOPA PET/CT significantly changed the therapeutic approach.

Conclusions In our series, ^{18}F-DOPA PET/CT was shown to be a highly sensitive tool in detecting multiple paragangliomas in genetically elated PGL syndromes, even without clinical or other signs of the disease, changing the therapeutic approach in 25% of all patients. According to our data, ^{18}F-DOPA PET/CT can be reasonably suggested as a "first-choice" examination, not only in patients already treated, during follow-up, but also in "only genetically-proven" patients, with no signs/inconclusive signs of the disease, to "map" the distribution of the lesions.

CARDIOVASCULAR 1

Prognostic value of combined myocardial perfusion imaging (MPI) and coronary calcium score (CCS) assessment: a 5-year follow-up study in patients with intermediate likelihood of coronary artery disease (CAD).

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Aim Nowadays hybrid SPECT-CT tomographs offer the opportunity to simultaneously evaluate both functional (MPI) and morphoanatomical (CCS) aspects of atherosclerosis. The aim of this study was to assess the possible additional prognostic value of CCS in adjunct to MPI in the evaluation of patients with intermediate risk of CAD.
Materials and methods The initial study population consisted of 367 prospective patients who were scheduled for MPI because of clinically suspected CAD and classified at intermediate risk as determined on the basis of the Framingham Risk Score. All subjects underwent simultaneous rest sestamibi MPI and CCS evaluation as a part of a standard two-day stress-rest MPI protocol. Studies were acquired with a SPECT-CT tomograph equipped with diagnostic multislice CT (Symbia T2, Siemens Medical Solutions, Erlangen, Germany). Summed stress scores (SSS) and Agatston data were calculated for all patients and MPI studies were considered "positive" (+) if SSS value was greater than 3. Subjects were divided into four groups on the basis of test results: MPI- and CCS<400 (group A), MPI- and CCS≥400 (group B), MPI+ and CCS<400 (group C), and MPI+ and CCS≥400 (group D). Follow-up data were collected through telephone interview. Patient groups were compared using the Student's t test for continuous variables and the chi-square or Fisher's test for proportions. Survival curves were generated using the Kaplan-Meier method and compared applying the log-rank test.
Results Fifteen patients were excluded because of sub-optimal quality of MPI and/or CCS studies and a further 22 subjects did not complete the follow-up. The remaining 330 patients (216 men, mean age 67±12 years) were prospectively followed up for an average of 63±9 months and the outcome events considered were: the hard end points of cardiac death and non-fatal myocardial infarction and the soft end points of hospitalization for unstable angina or late (>90 days) coronary revascularization. Group A consisted of 126 patients, group B of 58, group C of 32, and group D of 114. The cardiac event rate in the study population was 2.7%/year. Annual event rates for overall cardiac events in groups A, B, C and D were 0.3, 1.4, 4.4 and 5.6%/year, respectively. Patients with a normal MPI had higher survival free of cardiac events ($p<0.01$); additionally an increase in global chi-square in predicting all cardiac events occurred when CCS data were added to MPI information. Kaplan-Meier curves showed a significant difference in event-free survival at 5 years in the four groups and, interestingly, the risk for cardiac events in patients with a normal MPI but different CCS values (group A vs B) was similar after 3 years, while the difference became significant at the end of follow-up period.
Conclusions Although this study has several limitations it shows that a "hybrid" approach, combining an anatomical assessment of coronary atherosclerotic plaque burden (which probably better estimates longer-term prognosis) with a functional evaluation of myocardial ischemia (more closely related to "short-term risk"), may help to refine temporal risk stratification among subjects with an intermediate likelihood of CAD. Multicenter controlled prospective trials are required to confirm these preliminary findings and to assess their potential impact in larger clinical settings.

Incremental prognostic value of myocardial perfusion SPECT in asymptomatic diabetic patients

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Aim Stress myocardial perfusion single-photon emission computed tomography (MPS) has assumed a central role in the diagnosis, evaluation and management of cardiovascular disease in patients with diabetes mellitus. Risk reclassification methods are more clinically appealing and easier to understand than other analytical approaches. No reports have explored the comparative ability of stress MPS risk markers using varied iterative and risk classification approaches in asymptomatic diabetic patients. The aim of the current study was to assess the incremental prognostic value of MPS in asymptomatic diabetic patients and to estimate cardiac death or non-fatal myocardial infarction (MI) using traditional prognostication approaches and more recent methods. We also set out to assess the temporal characteristics of cardiac risk according to gated MPS findings.
Materials and methods The study population included asymptomatic patients with type 2 diabetes mellitus referred for MPS as part of the Impact of inDucible Ischemia by Stress MPS (IDIS) investigation. Of the patients enrolled in the IDIS trial, 450 were selected for the purposes of the present investigation. As part of the baseline examination, clinical teams collected information not only on diabetes and its complications, but also on traditional cardiovascular risk factors. From these clinical variables the pre-test CAD likelihood was calculated for each patient using dedicated software (Cadenza, Advanced Heuristics, Inc., Bainbridge Island, Washington). All patients underwent same-day sestamibi rest and stress gated MPS with exercise or dipyridamole stress test, according to the recommendations of the European Association of Nuclear Medicine and European Society of Cardiology. An automated software program (Cedars-Sinai Medical Center, Los Angeles, CA) was used to calculate left ventricular ejection fraction (LVEF) and scores incorporating both the extent and severity of perfusion defects. A multivariable Cox proportional hazards model was employed to estimate cardiac death and non-fatal MI. The net reclassification improvement (NRI) was calculated and parametric survival analysis was used to predict time to events.
Results On univariable Cox analysis, pre-test CAD likelihood ($p<0.05$), post-stress LVEF ($p<0.001$), and summed stress score ($p<0.001$) were significant predictors of cardiac death and MI. On multivariable analysis, post-stress LVEF ($p<0.05$) and summed stress score ($p<0.05$) were independent predictors of events. The addition of MPS perfusion data significantly improved the prognostic power of a model including clinical and LVEF, increasing the global chi-square value from 28.7 to 70.0 ($p<0.001$). The addition of MPS data resulted in reclassification of 54.82% of the sample. The reclassification was correct in 195 and incorrect in 44 patients (81.58% and 18.41% of the reclassified patients, respectively) with a NRI of 0.25 (95% confidence interval 0.06-0.44; $p<0.01$). The parametric survival analysis showed the highest probability of cardiac death or MI and the shortest time to events in patients with abnormal MPS and post-stress LVEF ≤45%.
Conclusions The present study showed that in stress MPS performed in asymptomatic diabetic patients, analytical approaches able to establish a reclassification of events may contribute to improved estimation of outcomes. Post-stress LVEF and stress-induced ischemia by gated MPS also influenced the temporal characteristic of patient risk at long-term follow-up.

GSPECT evaluation of left ventricular function using a CZT camera and a fast low-dose clinical protocol: comparison with magnetic resonance imaging

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Background CZT technology allows ultrafast low-dose myocardial scintigraphy but its accuracy in measuring left ventricular ejection fraction and volumes is still to be defined.
Materials and methods To this purpose, 55 patients (23 females, mean age 63 ± 9 years) referred for myocardial perfusion scintigraphy were studied at rest using a CZT camera (NM530c, GE Healthcare) and a low-dose ^{99m}Tc-Tetrofosmin clinical protocol (mean dose 319 ± 83 MBq). Myocardial GSPECT imaging was performed as a 4-min acquisition in list mode, 15 min after radiotracer injection. Images were reframed (8/16-frame) using Lister software on an Xeleris workstation (GE Healthcare) and then reconstructed with a dedicated iterative algorithm (Myovation for Alcyon, GE). Left ventricular function analysis was performed using quantitative gated SPECT (QGS) software. Within 2 weeks patients underwent cardiac magnetic resonance imaging (MRI) (1.5 T unit Cvi-GE Healthcare) using a 30-frame acquisition protocol and dedicated software for analysis (MASS 6.1, Medis).
Results QGS 8-frame analysis showed an excellent correlation with MRI volumes [End Diastolic Volume (EDV): r= 0.90; End Systolic Volume (ESV): r= 0.94, p<0.001] but significant underestimation of measurements (EDV mean difference:-39.5 ± 9 mL; ESV: -15.4 ± 5 mL, p<0.001). Similarly, QGS 16-frame assessment showed an excellent correlation with MRI volumes (EDV: r= 0.92; ESV: r= 0.95, p<0.001) but significant underestimation of measurements (EDV mean difference:-33.1 ± 9 mL; ESV: -17.9 ± 6 mL, p<0.001). QGS 8-frame mean ejection fraction (EF) was found to be closely correlated with MRI (r= 0.84, p<0.001) despite significantly lower values (47.9 ± 16 % vs 51.2 ± 15 %, p<0.008). QGS 16-frame mean EF showed the best correlation with MRI (r= 0.91, p<0.001) and values similar to mean MRI values (49.7 ± 16 %, p=ns). Regional analysis showed a good correlation between both 8/16-frame summed motion score and MRI wall motion score index (8-frame summed motion score: r= 0.78; 16-frame summed motion score: r= 0.82; p<0.01).
Conclusions Low-dose GSPECT with a CZT camera provides ventricular volumes that correlate well with MRI despite significant underestimation of measurements. 16-bin framing appears more accurate than 8-bin framing in EF estimation.

Reproducibility of I-123 metaiodobenzylguanidine myocardial scintigraphy in patients with advanced heart failure

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Aim Myocardial scintigraphy with I-123 metaiodobenzylguanidine (MIBG) is widely used for risk stratification of patients with heart failure. However, few data are available about the reliability of this technique. The aim of this study was to assess the reproducibility of planar I-123 MIBG myocardial scintigraphy in patients with severe left ventricular (LV) systolic dysfunction.
Material and methods Seventy-four patients (62 men, mean age 67±10 years) with documented severe LV dysfunction (LV ejection fraction 30±7%) underwent planar I-123 MIBG cardiac sympathetic imaging. In all patients, following thyroid gland blocking with potassium iodide, 111 MBq of I-123 MIBG was intravenously injected. Planar imaging in the anterior view was obtained 15 minutes (early) and 4 hours (delayed) after the tracer injection using a dual-head gamma camera equipped with a low-energy, high-resolution collimator. A preset time of 10 min was used for image acquisition with a 159±10 keV of energy window. Myocardial MIBG uptake was semi-quantified by calculating H/M ratio after drawing regions of interest over the entire heart and upper mediastinum on early and delayed planar images. Intraobserver reproducibility was measured by comparing the images interpreted twice by the same reader and interobserver reproducibility was measured by comparing the images interpreted by two different readers. The intraclass coefficient of correlation (ICC), the Lin's concordance correlation coefficient (CCC), and the Bland-Altman method were employed to determine the reproducibility of H/M ratios. For ICC, a two-way mixed-effects model was used. Bland-Altman plots were used to evaluate the correlations between the measured values. The sample size was calculated assuming an ICC of at least 0.75 and accepting a 95% confidence interval (CI) width of the ICC of 0.20, and 70 patients was found to be sufficient. All statistical analyses were performed using the Stata software package, version 12.1.
Results Intra- and interobserver analyses showed excellent agreement for the measured early and delayed H/M ratios on planar I-123 MIBG images (ICCs for the early H/M ratios were 0.97 and 0.96 and for the delayed H/M ratios 0.97 and 0.95, respectively). The intraobserver CCC was 0.95 for both early and delayed H/M ratios. The interobserver CCC was 0.92 and 0.91 for early and delayed H/M ratios, respectively. The intraobserver Bland-Altman 95% limits of agreement were -0.11 to 0.14 for the early H/M ratios with a mean difference between the two readings of 0.015±0.064, and -0.12 to 0.14 for the delayed H/M ratios with a mean difference between the two readings of 0.014±0.066. The interobserver Bland-Altman 95% limits of agreement were -0.11 to 0.18 for the early H/M ratios with a mean difference between the two readers of 0.035±0.073, and -0.12 to 0.19 for the delayed H/M ratios with a mean difference between the two readers of 0.039±0.080.
Conclusions The present study showed a high reliability of planar I-123I MIBG myocardial scintigraphy in patients with severe LV dysfunction. These findings confirm that MIBG cardiac imaging can be implemented easily for clinical risk stratification in heart failure.

Early I-123 MIBG cardiac wash-out: feasibility of dynamic 3D kinetic analysis using a CZT ultrafast camera

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Background To date, no data are available in the literature concerning 3D 123-MIBG kinetics in vivo.
Materials and methods To address this, 18 patients consecutively scheduled for I-123 MIBG cardiac scintigraphy were studied using a CZT camera (NM530c, GE) and dynamic acquisition in list mode simultaneously started with bolus injection of the radiotracer (185-370 MBq) for an overall duration of 900 sec. A temporal series of 3D axial volumes (70x70x50 voxels, 4x4x4 mm) was reconstructed from acquired raw data, using filtered back-projection. Thirty 3D volumes were generated integrating 5-sec time frames, for a total duration of 150 sec. A global cardiac image was also reconstructed, integrating the signal over the full acquisition time (900 sec) as the reference one for myocardial wall delineation. Images in DICOM format were transferred to a workstation for image analysis by HIPPO MIBG® software. Blood pool (BP) and left ventricle wall (LV) volumes of interest (VOIs) were manually drawn in order to cover the whole LV. Due to the nature of the reconstruction process, drawn VOIs were automatically reported on the reframed volumes that are aligned with the global volume. Time-activity curves (TAC) were extracted for LV by averaging the signal intensity in the respective VOI in each time frame. Hence, a 30-point TAC was obtained for each patient. LV curves were fitted to

a bi-compartmental model defined as f(t)=g(t)+c(t) where c(t)=P6*e$^{-P7*(t-P5)}$- e$^{-P3*(t-P1)}$. Curve fitting was performed using the Levenberg-Marquardt algorithm. MSI (maximum signal intensity), MUS (maximum up-slope), TTP (time to peak), and MTT (mean transit time) parameters and ΔWash-out (increase of the signal from MSI point to last frame in percentage) were obtained.
Results TAC curve analysis was feasible in 16/18 patients (89%). MSI values in the second compartment ranged from 7.7 to 25.4 normalized counts/voxel (mean 14.5±5.6). MUS values ranged from 0.85 to 3.53 normalized counts/voxel/sec (mean 1.7±0.74). ΔWash-out values ranged from 0 to 9.9% (mean 2.96±3.36%). All parameters showed a normal distribution in the study population.
Conclusions Analysis of TAC curves of I-123 MIBG is feasible using CZT technology and dynamic 3D acquisition. These preliminary results suggest that I-123 MIBG myocardial wash-out is an early phenomenon to be considered in clinical practice.

CARDIOVASCULAR 2

Comparison of myocardial blood flow quantification for $^{13}NH_3$ and 3D-PET using different image reconstruction algorithms (3D reprojection, 3D OSEM, 3D OSEM with time-of-flight and 3D point spread function) and De Grado Model

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Aim To compare the absolute quantification of myocardial blood flow (MBF) with $^{13}NH_3$ and 3D PET using different image reconstruction algorithms (3D reprojection, 3D OSEM, 3D OSEM with time-of-flight and 3D PET point spread function) and the De Grado Model.
Materials and methods Twenty-two patients with different pathologies (hypertension, CAD, hypertrophic and dilated cardiomyopathy) underwent 3D PET (Discovery-690; GEMS, Milwaukee, USA) at rest and during vasodilatory stress after dipyridamole infusion (0.56 mg/kg/4 min). After the injection of 370 MBq of $^{13}NH_3$, a 3D-PET dynamic scan was acquired with framing: 9x10s, 6x15s, 3x20s, 2x30s, and 1x900s. Off-line the 3D PET data were reconstructed using different reconstruction algorithms and parameter configurations as follows: (**a**) 3D reprojection, with the smallest possible filter imposed by the Nyquist limit, 3D OSEM with two different numbers of iterations: (**b**) 3 iterations and (**c**) 5 iterations, and (**d**) 3D OSEM also accounting for time-of-flight and 3D PET point spread function. Quantification was performed with PMOD software (v3.1, PMOD Technologies, Zurich) using the De Grado 1-compartment model. Two analyses were conducted. At first, VOIs of the blood pool and myocardial tissue were drawn on images **a**; subsequently they were applied to reconstructions **b**, **c**, and **d**. In the second analysis, new VOIs were drawn on each differently reconstructed image set, in order to evaluate whether the reconstruction method could affect the delineation of the VOIs. Comparisons were made using Bland-Altman plots.
Results The analysis performed using the same VOIs showed no significant mean difference between methods **a** (used as reference), **b** and **c**. With method **d** a mean difference of +5% was observed. Standard deviations between the chosen reconstruction and **a** methods were [rest,stress]: **b**[4.5%,6.5%], **c**[4.2%,6.1%], **d**[5.5%,9.2%]. Using different VOIs the analysis of mean differences gave identical results. The standard deviations, indicating the inter-algorithm variability, increased to **b**[8.2%,6.3%], **c**[7.1%,7.7%], **d**[7%,9.1%]. The spill-over fraction was minimized by method **d**: -20% compared to **a** and -31% compared to **b.** Method **c** had the same values as **a**.
Conclusions Absolute quantification of MBF with $^{13}NH_3$, 3D-PET and the De Grado model is consistently stable across different reconstruction methods. The most innovative reconstruction algorithm, including time-of-flight information and 3D PET point spread function, has slightly higher values compared with 3D-RP and uses less spill-over correction. The between-algorithms variability remained limited to less than 9%. Thus, MBF quantification can be considered clinically robust to different image reconstruction techniques.

Variability of global and regional FDG myocardial uptake in Hodgkin's lymphoma patients

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The normal physiological uptake of ^{18}F-fluorodeoxyglucose (FDG) in the heart is variable. Different uptake in myocardial tissue is frequently observed in fasting oncology patients, without heart disease, when clinical positron emission tomography (PET) studies are performed. This variability in FDG uptake has still not been explained. The aim of this study was to evaluate global and regional myocardial FDG uptake in non-diabetic cancer patients without heart disease, before and after chemotherapy (mean 2 weeks), in order to verify a possible relationship between therapy and FDG left ventricular uptake.
Twenty-nine consecutive patients (15 M, 14 F, age 37.3±10.2, weight 67±13 kg) newly diagnosed with biopsy-proven Hodgkin's lymphoma were included in this study. All patients underwent oncological and cardiological examinations, including echocardiogram, and high-resolution PET/CT studies (^{18}F-FDG activity 5.1±0.9 MBq/kg) after at least 8 hours of fasting. The first PET was performed before therapy and was repeated at least 2 weeks after chemotherapy. We performed a total of 99 studies. The chemotherapy treatment was the ABVD scheme, supplemented with BEACOPP in four patients. All patients were followed up for 30±11 months (max 46 months). Analysis of ^{18}F-FDG myocardial uptake was performed by means of the maximum standardized uptake value (SUVm), evaluated by drawing regions of interest (ROIs) on the septal (S), anterior (A), lateral (L) and inferior (I) walls, considering one short axis slice including the entire ventricular volume. A further ROI was drawn on the liver in each PET scan in order to normalize myocardial uptake to liver activity.
The ejection fraction value at staging was 62.7±3.6. On the first PET scan SUVm in the S, A and I walls was on average 95% of that in the L one: in detail, the SUVm values of the different walls were as follows: S wall: 4.6±3.7, A wall: 4.8±4.0, L: wall 5.0±4.2, and I wall: 4.7±3.8. The proportion between the walls did not change significantly on the second PET scans, while a within-subject time effect (a 30% increase in SUVm between first and second PET scans) was found for all the walls ($p<0.05$). No variation in liver activity, whose SUVm was 2.5±0.5, was found between different PETs ($p>0.05$). To date, no patient has developed cardiotoxicity.
Our preliminary data show a significant increase in FDG global ventricular uptake after chemotherapy, suggesting a direct influence of chemotherapeutic agents on myocardial glucose metabolism. All the patients will continue to be followed up during treatment, through oncological and cardiologic examinations and PET scans, in order to

look for possible correlation between this variation and clinical and pharmacological data, as a possible predictive factor of cardiotoxicity.

The role of ^{18}F-FDG PET/CT in relation to histological status in the assessment of patients with carotid plaques

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Aim Inflammation, plaque erosion and embolism are the main causes of acute cardiovascular events, which usually result from the sudden rupture of macrophage-rich atherosclerotic plaques. The interior of a plaque is an anaerobic area, therefore glucose is the major substrate for macrophages. The aim of this study was to look for a relationship between ^{18}F-FDG uptake on PET/CT and histology of carotid artery plaques.
Materials and methods Thirty-one patients with an ultrasound diagnosis of carotid plaque with stenosis of at least 70%, candidates for endarterectomy, underwent ^{18}F-FDG PET/CT. Plaques, removed during carotid endarterectomy, were histologically analyzed. Arterial ^{18}F-FDG uptake in the neck was measured by drawing a region of interest (ROI) around the artery on every slice of the co-registered transaxial PET/CT images. On each image slice, the SUV max and SUV mean of ^{18}F-FDG in the ROI (containing the arterial wall and the lumen) was calculated as the maximum pixel activity. We also calculated SUV max in coronal and sagittal PET/CT images. In addition, we calculated the maximum target-to-background ratio (TBR max) as the SUV max normalized to venous SUV max (measured by drawing a ROI around the superior vena cava), and the mean target-to-background ratio (TBR mean) as the SUV mean normalized to the venous SUV mean. Histological analysis identified plaques with inflammation, a thin overlying fibrous cap, calcification and fibro-fatty infiltration.
Results Analysis of our data showed a SUV max range of 1.2 to 4.2, and TBR range of 0.8 to 1.9. Of 17/31 patients found to have a plaque with fibro-fatty infiltration, 13 (77%) had a SUV max > 1.6 and 16 (94%) a TBR > 0.9. No statistically significant differences in SUV max value and TBR max value were found in relation to inflammation, calcification and fibrosis (presence/absence). A statistically significant difference was observed in TBR mean value in relation to presence versus absence of fibro-fatty infiltration (1.50 vs 1.25; t=2.05, p=0.05). A statistically significant difference was observed in TBR mean value in relation to a BMI of 25 to 29 (1.47 vs 1.12; t= 2.57; p= 0.02). A statistically significant Pearson's correlation was observed between SUV max of carotid plaque and SUV max of aortic arch (r= 0.793, p= 0) and between SUV mean of carotid plaque and SUV mean of aortic arch (r= 0.838,p= 0)
Conclusions Our results show an association between plaque FDG uptake, evaluated in particular with TBR mean, and fibro-fatty infiltration and underline the presence of vascular inflammation, predominantly in the form of macrophages. We confirm the role of PET imaging as a biomarker for the metabolic activity of atherosclerosis. ^{18}F-FDG PET/CT is able to identify symptomatic lesions and could help to identify patients at high risk of cardiovascular events. Future applications might include the prediction of plaque rupture and clinical events and a role in monitoring the response of atherosclerosis to therapy.

^{18}F-fluoride-based molecular calcium deposition as biomarker of early and ongoing molecular calcification in the vascular walls in low, intermediate, and high cardiovascular risk subgroups

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Aim To evaluate the potential of ^{18}F-fluoride PET/CT to detect early and ongoing molecular calcification within the vascular walls.
Methods The present study included 80 oncology patients (20 males, mean age 65.3±8.2 range 26-81) who underwent ^{18}F-fluoride PET/CT imaging in the course of follow up for either breast or prostate cancer. Not long before imaging, all patients were administered a questionnaire for cardiovascular risk stratification, which was a simplified version of the Framingham model (including age, diabetes, smoking, systolic blood pressure and BMI). The whole study group was thus subdivided into three risk categories: low (<10%, n=23), intermediate (10% to 20%, n=35), and high (>20%, n=22). In each patient, volumetric regions of interest (ROI) were drawn on two aortic segments (thoracic and abdominal aorta), and on the subclavian, carotid, iliac and femoral arteries, respectively. In these regions, average ^{18}F-fluoride uptake was measured and normalized for blood-pool radioactivity drawn within the inferior vena cava to obtain regional and mean target-to-background ratios (TBRs). The degree of arterial calcification was measured in the same arterial districts. For this purpose, we used a dedicated software (Osirix) providing Agatston scores whose values were adjusted to account for slice width. Intergroup differences in regional and arterial TBRs and calcium scores were tested using Student's t test for unpaired data. P values <0.05 were considered significant.
Results The high cardiovascular risk subgroup showed higher mean TBR (1.8±0.5 vs 1.3±0.6; p<0.0001), total calcified segments (CS) (2500±864 vs 1576±703; p<0.01), and both TBR and CS in the abdominal aorta (p<0.006 for TBR; p<0.02 for CS) and carotid arteries (p<0.0001 for TBR, p<0.04 for CS) with respect to the low cardiovascular risk subgroup. Similarly, comparison of both high vs intermediate and intermediate vs low risk profiles highlighted significant differences in mean TBR (p<0.001) and TBR of the abdominal aorta (p<0.04 and p<0.02 respectively) and carotid arteries (p<0.03 and p<0.001 respectively). On the contrary no significant differences were highlighted in the total and regional CS of high vs intermediate and intermediate vs low risk groups. In the whole group of patients calcified segments showed similar TBRs with respect to non-calcified arterial walls in the abdominal aorta, while in the carotid arteries, TBR was significantly higher in calcified segments.
Conclusions The present study is consistent with the notion that PET/CT imaging of fluoride uptake can identify early molecular stages of arterial calcification. This phenomenon precedes morphological evidence of calcium burden on conventional CT imaging. In particular, the better risk stratifications obtained with TBR evaluation of NaF uptake fits with the concept that arterial calcification is an active process in which small calcium crystals appear early in the course of atherosclerosis and aggregate to large (CT-detectable) hydroxyapatite crystals only late in the disease course. Further studies are needed to specifically investigate the role of this promising technique in the management of patients with suspected atherosclerosis.

Heart transplant recipients: from myocardial deformation to myocardial perfusion

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Background Chronic immunological responses appear to be the cause of occlusive long-term cardiac allograft vasculopathy (CAV) in heart transplant (HTx) recipients. Even though chronic rejection is still the major obstacle to a long-term positive outcome after HTx, it remains unclear whether mild, diffuse intimal thickening in the epicardial arteries of HTx recipients affects the functional status of the coronary tree. Coronary angiography (CCA), nuclear myocardial perfusion and left ventricular (LV) function assessment are therefore of paramount importance in HTx patients. Moreover, during long-term follow-up, speckle tracking echocardiography (STE) allows comprehensive assessment of LV regional function, compared with traditional 2D echocardiographic LV functional assessment parameters.
Aim To describe the normal values for systolic longitudinal strain and synchrony by STE in HTx recipients showing preserved LV ejection fraction (LVEF) and no clinically significant complications, compared with controls, and to evaluate the diagnostic efficacy of cardiac ^{82}Rb PET/CT in predicting CAV development and in improving understanding of STE results, with a view to obtaining optimal management of HTx pts.
Methods 115 relatively stable HTx patients (71 males; 58.3±5.8 years; 7.8±4.5 years after transplant) and 80 healthy age- and sex-matched controls underwent standard echocardiography and LV STE focused on the LV analysys. Strain in all LV segments was averaged to obtain a global value: global longitudinal strain (GLS). For all 115 Htx pts, fast protocol rest-dypiridamole (50mCi R/D) ^{82}Rb PET/CT scans (Biograph 16, Siemens) were also obtained and images visually and semi-quantitatively analyzed (AutoQuant-QPS). CT was used for attenuation correction and calcium score (CAC) evaluation. 82Rb findings were compared with qualitative CCA. Obstructive CAD was considered in cases with >70% diameter stenosis.
Results Mean systemic blood pressure (sBP) was significantly higher in HTx patients ($p<0.01$); LV diameters and LVEF did not significantly differ between the two groups (57.4±4.4 in HTx vs 58.5±4.8 % in controls, p = NS), while mass index was increased in HTx ($p<0.01$). Mean GLS was lower in the HTx group vs controls (13.5±2.3 % vs 18.3±3.3 %; $p< 0.001$). These variables were useful for differentiating between groups (area under the curve: 0.88 for GLS < 16%). Differences remained significant after adjustment for other clinical variables. On multivariable analysis, age at HTx ($p<0.001$) and sBP average ($p<0.01$) emerged as the only independent determinants of LV GLS in HTx. Despite a drop in deformation indexes, ^{82}Rb PET/CT showed no transient or chronic ischemia (SDS-SRS <2) in 83/115 HTx patients. Fixed perfusion defect (SRS>4; extent>5%) was found in 20/115 pts and reversible ischemia (SDS>4) in the last 12/115, showing coronary stenosis on CCA. Moreover, on CT analysis, no evidence of abnormal CAC was found in any of the HTx pts, confirming that in these pts atherosclerosis changes are less likely than chronic rejection.
Conclusions Despite LV performance impairment along the long axis suggested by 2D STE, the lack of significant myocardial perfusion defects in HTx patients with normal LVEF supports the hypothesis of a chronic progressive phenomenon, strongly associated with the time from heart transplant and with the increase in mean blood pressure secondary to immunosuppressive therapies during the follow-up. The associated impairment of perfusion and STE data can modify patient management, suggesting conventional CCA control.

NEUROLOGY 1

Effective brain connectivity in *GRN*-related monogenic frontotemporal dementia: a path modeling analysis

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Background It has been suggested that monogenic frontotemporal dementia (FTD) due to Granulin (GRN) mutations presents a specific pattern of atrophy, involving parietal regions, as compared to *GRN*-negative FTD. Recent literature has suggested that study of functional neural networks, rather than regional structural damage, might better elucidate the underlying pathogenic mechanisms, showing a complex relationship between structural alterations observed with conventional neuroimaging techniques.
Objective To evaluate effective brain connectivity in FTD patients carrying *GRN* mutations (FTD GRN+) as compared to FTD patients without pathogenetic *GRN* mutations (FTD GRN-), and healthy controls (HCs).
Methods Thirty FTD patients (15 GRN+ and 15 GRN-, matched for age, gender and clinical phenotype) and 15 age- and gender-matched HCs underwent brain perfusion single-photon emission tomography at rest. Brain regions specifically involved in FTD, i.e. dorsolateral cortex, anterior cingulate cortex, orbitofrontal cortex, posterior temporal cortex, temporal pole, and parietal cortex, were used as volume-of-interest (VOI) to identify functionally interconnected areas using voxel-wise covariance analysis. A path model was defined by means of effective connectivity analysis within the Bayesan modeling and structural equation modeling framework. Testing for statistically significant differences between the three groups on the identified model was carried out.
Results The best fit was obtained by the data-driven approach, and brain connectivity pathways resembling the state-of-the-art anatomical knowledge were obtained. The signature of FTD (both GRN+ and GRN- subgroups) was the disconnection of dorsolateral and temporal cortices, as compared to HC. When GRN+ and GRN- groups were considered, the former presented a selective bilateral parieto-temporal disconnection in respect to GRN- patients. Furthermore, in the FTD GRN+ patients, an increased compensative connectivity of the temporal regions, i.e. temporal pole and posterior temporal cortices, was observed.
Conclusions The present work suggests that impairment of effective functional connectivity of the parieto-temporal regions is the hallmark of *GRN*-related FTD. Compensatory mechanisms, which should further investigated, may however occur.

Neural reserve and neural compensation components of "cognitive reserve" in prodromal Alzheimer's disease patients: A European Alzheimer's Disease Consortium (EADC) project

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Aim This project aimed to investigate the functional basis of resilience to neurodegeneration (cognitive reserve, CR) in highly educated patients with prodromal Alzheimer's disease (pAD) and to elucidate whether in these patients CR represents the preservation of physiological networks of highly-educated normal subjects (neural reserve) or rather the recruitment of alternative networks in the presence of brain damage (neural compensation).
Methods Sixty-four patients with amnestic mild cognitive impairment converted to AD dementia during follow-up and 90 controls underwent brain FDG-PET. Both groups were divided into poorly educated (n=42 controls and n=36 pAD) and highly educated (n=48 controls and n=28 pAD) subgroups. In a previous study we compared brain metabolism between education-matched groups of patients and controls and confirmed the hypothesis of more extended hypometabolism in highly educated pAD patients. Then we compared brain FDG PET of highly and poorly educated pAD patients in both directions to identify regions of high education-related metabolic depression and compensation. In the present study, the cluster of significant compensation, mainly corresponding to the right dorsolateral-prefrontal cortex (DLFC),was further used as volumetric region of interest (VROI) in a brain interregional correlation analysis to explore metabolic connectivity in each pAD subgroup. We then performed the same metabolic connectivity analysis of the right DLFC in highly educated controls (CTR) to provide evidence on whether the metabolic correlations highlighted in highly educated pAD represent the preservation of physiological networks of highly-educated normal subjects (neural reserve), the recruitment of alternative networks (neural compensation), or a combination of the two. All analyses were performed using SPM8 ($p<0.001$ uncorrected at peak-level, $p<0.05$ FDR-corrected at cluster-level; age, gender, MMSE score and center as nuisance).
Results In highly educated pAD, the DLFC showed wide metabolic correlations with several cortical areas in both hemispheres (fronto temporal cortex, parahippocampal gyrus and precuneus) while it was substantially only autocorrelated in poorly educated pAD. In highly educated CTR the right DLFC showed a similar distribution of metabolic correlations as in highly educated pAD but it was moderately less extended. In LE-CTR the metabolic connectivity of right DLFC was markedly reduced, as it was substantially autocorrelated and then just correlated with small clusters in precuneus, occipital and limbic cortex mainly in the ipsilateral hemisphere.
Conclusions The present findings suggest that highly educated pAD individuals can cope better with the disease thanks to neural reserve but also to the recruitment of compensatory neural networks in which the right DLFC plays a key role. Accordingly, these data support the view of 'cognitive reserve' as a phenomenic construct based on both neural reserve and neural compensation.

Brain perfusion in hereditary coproporphyria (HCP) evaluated by ^{99m}Tc-bicisate (Neurolite) single-photon emission computed tomography (SPECT)

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Background and aim Hereditary coproporphyria (HCP), the second most common form of porphyria, is an autosomal dominant disorder caused by deficiency of the enzyme coproporphyrinogen oxidase and characterized by abdominal pain, neurological symptoms and psychiatric disorders and, in some cases, by cutaneous findings similar to those observed in porphyria cutanea tarda. SPECT brain perfusion studies in HCP are lacking. The aim of our retrospective research was to investigate the SPECT cerebral perfusion pattern in HCP patients.
Patients and methods Seven patients already diagnosed with HCP (3 F, 4 M, mean age 44 + 19.6 y; age range 16-83 y) underwent brain perfusion SPECT. The patients belonged to two families, composed of the mother + 4 sons and the mother + 1 son respectively. SPECT studies were started 30-45 minutes after the intravenous injection of 740 MBq of ^{99m}Tc- N,N'(1,2-ethylenedyl)bis-L-cysteine diethylester (^{99m}Tc-Bicisate i.e. Neurolite, otherwise known as ECD). In three patients the scintigraphic study was repeated after 3, 10 and 21 months, respectively. All the studied subjects were inpatients admitted for an abdominal pain crisis. All the studied subjects underwent an electromyographic and a magnetic resonance (MR) and/or computed tomography (CT) study. All SPECT images were retrospectively evaluated by two experienced observers and agreement was reached in all cases.
Results All patients showed brain perfusion defects on SPECT study. The perfusion pattern was quite varied ranging from the presence of multiple bilateral mild cortical perfusion defects to moderate side cortical perfusion asymmetry and small perfusion defects. The most commonly affected areas were the temporal lobes (all 7 patients), frontal lobes (6 patients), and parietal lobes (4 patients). Occipital lobe, basal ganglia and cerebellar involvement was never observed. In the three subjects in whom the SPECT study was repeated, modifications of the perfusion pattern were observed, with recovery of hypoperfused areas and appearance of new perfusion defects in other brain regions. In all patients electromyography was normal, as were MR and CT studies.
Discussion and conclusions SPECT demonstrated brain perfusion defects in all HCP patients despite normal patterns on electromyographic, MR and CT studies. The perfusion abnormalities found were usually mild to moderate, which probably explains the normal pattern observed on MR and CT studies. Compared with these techniques, therefore, SPECT with ^{99m}Tc offers the advantage of a far greater sensitivity in HCP patients. Temporal, parietal and frontal lobe cortical involvement was common. The reversibility and the changes over time in the perfusion defects demonstrated in the three subjects in whom the study was repeated suggests that a dynamic component (spasm?) might contribute to the psychiatric and neurological symptomatology observed in HCP patients, in line with what has already been observed in acute intermittent porphyria. We hope that this new insight into the pathophysiology of HCP might pave the way for improvements in its clinical pharmacology.

The prognostic value of qualitative and semi-quantitative analysis of cerebral blood flow changes after unilateral chronic subdural hematoma evacuation

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Background Chronic Subdural Hematoma (CSH) constitutes one of the most frequent neurological diseases in adults, still beard by poor prognosis. Signs and symptoms are related to compression of the underlying cortical areas and reduced regional perfusion. ^{99m}Tc-HMPAO SPECT gives analysis of CBF, and allows to visualize flow redistribution. To date, few studies have set out to evaluate, in CSH, preoperative cerebral perfusion and changes after CSH treatment.
Materials and methods Fifteen patients, 11M and 4F, ranging in age between 78 and 82 years (mean 80.6), underwent unilateral CSH evacuation. Patients were submitted to preoperative (day -1), and early (day 2-3) and late (day 7-8) postoperative cerebral ^{99m}Tc-HMPAO SPECT. Scans (magnification 1, matrix 128x128; 180° rotation, a 3° step and shoot technique; 30s per frame) were obtained by dual-headed gamma camera equipped with low-energy high-resolution parallel-hole collimator. CBF was assessed both qualitatively (comparing ipsilateral vs contralateral cortex) and semi-quantitatively [using the asymmetry index (AI) ratio]. Results were statistically evaluated and compared with final prognosis, based on Glasgow Outcome Scale (GOS) score.
Results and conclusions Preoperative qualitative analysis showed relative hypoperfusion of the cortex ipsilateral to the hematoma in all patients. This finding was confirmed by the semi-quantitative AI ratio ($p < 0.05$). Specifically, CBF demonstrated an inhomogeneous ipsilateral pattern with alternation of hypoperfused areas and regions with preserved blood flow. Early SPECT study, evidenced a significative postoperative hyperperfusion limited to the ipsilateral cortex ($p < 0.01$). This pattern resulted in higher perfusion at the level of the previously hypoperfused areas, in comparison with the contralateral structures. Moreover, the postoperative late SPECT control on day 7-8 after surgery demonstrated the progressive re-expansion of the compressed ipsilateral cortex, and the attenuation of the differential of CBF in both hemispheres, with a definitive homogeneous balancing of the pattern. It is noteworthy how the contralateral areas not involved from the presence of the hematoma, when preoperatively hypoperfused, showed a relative hyperperfusion at the postoperative control, and, conversely, if relatively hyperperfused before the operation, evidenced a postoperative reduction of flow, as the cerebrovascular autoregulation has been maintained. This findings were related in each case with an improvement of the clinico-neurological symptoms and a good outcome at the GOS. In two cases, qualitative observation showed a preoperative ipsilateral cortex perfusion pattern similar to that of the "good recovery group", but the semi-quantitative analysis showed higher AI ratio values (-2.6% vs -15.6%). The postoperative early SPECT control demonstrated a significant relative hyperemia ($p < 0.01$), with ipsilateral values higher than those of the "good recovery group", versus contralateral relative hypoperfusion. The late SPECT control showed a global hypoperfusion pattern as for ischemia. Likewise, the neurological outcome worsened, being characterized by significant alterations of consciousness, coma, and, finally, death. Our study, although only qualitative and semi-quantitative, and performed on a limited case number, demonstrates that postoperative hyperemia is due to physiological cerebrovascular autoregulation. Moreover, we showed that redistribution of the CBF involves the cerebral cortex globally, indicating that vessel autoregulation remains unaltered even in the presence of a compressive mechanism. A significant impairment of CBF autoregulation led to worse outcome. Our study provides a modern pathophysiological interpretation of the cerebral dysfunction observed in patients affected by CSH, with prognostic implications.

The role of ^{18}F-FDG PET/CT in the assessment of epileptogenic focus in medically intractable epilepsy: comparison with invasive and non-invasive techniques and prognostic value

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Background Neurosurgery is an effective treatment option for patients with epilepsy refractory to anti-epileptic drugs, even in the presence of neocortical epilepsy. The achievement of a good post-surgical outcome is related to precise definition of the epileptogenic focus. Despite the number of clinical tools available, accurate focus localization remains a challenge.
Aim Our aim was to test the capability of qualitative and semi-quantitative analysis of ^{18}F-FDG PET/CT to establish the epileptogenic focus and predict the post-surgical outcome.
Materials and methods Fifteen patients with epilepsy underwent neurosurgery after a complete pre-surgical evaluation with MRI, PET/CT, scalp-EEG (electroencephalogram), video-EEG and, in some cases, stereo-EEG (SEEG). Qualitative analysis of PET/CT was performed visually by two expert nuclear medicine physicians, while semi-quantitative analysis was performed using SPM2 software (Standard Parametrical Mapping; Wellcome Department of Cognitive Neurology, London, UK). All patients were clinically evaluated after surgery and patients with more than 12 months follow-up were assigned Engel outcome ratings.
Results Nine patients had temporal lobe epilepsy (TLE) and six had extra-temporal epilepsy (ETE); histological specimens were available for 14 patients: 5 had mesial temporal sclerosis (MTS), 1 focal cortical dysplasia (FCD) type Ia, 1 FCD type Ic, 2 FCD type IIa, 2 FCD type IIb and 3 FCD type IIIa. MRI scan was positive in 73.3% of cases (88.8% of the TLE patients and 50% of the ETE patients); PET/CT was positive in 93.3% of cases (100% of the TLE patients and 83.3% of the ETE patients). Semi-quantitative analysis of PET scans demonstrated the presence of remote hypometabolism (RH) in 10 patients, whereas qualitative evaluation detected RH in only two patients. SEEG was performed in four ETE patients: among these, MRI was positive in one patient, while PET/CT was diagnostic in all cases. Six patients reached 12 months' follow-up: three were assigned to Engel class Ia, two to class Ib, and one to class III. Only one of the Ia patients had RH at SPM2 evaluation, while all the class Ib and class III patients had RH.
DISCUSSION. Our data confirm that ^{18}F-FDG PET/CT is an effective non-invasive tool for pre-surgical evaluation of TLE patients, showing a high sensitivity; moreover ^{18}F-FDG PET/CT allowed detection of the epileptogenic focus in patients affected by ETE, showing a sensitivity of 88.8%, whereas MRI had a sensitivity of 50%. SEEG results were consistent with those of PET. Epilepsy patients may be referred for surgery if there is agreement between clinical, electrical study and PET scan data, avoiding the need for intracranial electrode implantation. Although only a small proportion of the patients reached 12 months of follow-up, our results suggest a trend toward the importance of RH for prognosis: Engel class Ib and III patients had RH on semi-quantitative PET analysis. When the PET scan shows the presence of RH, then an SEEG evaluation can be considered.
Conclusions ^{18}F-FDG PET/CT shows high sensitivity in detecting the epileptogenic focus in both TLE and ETE patients; the presence of RH seems to have an impact on post-surgical outcome; semi-quantitative analysis appears to be crucial to define the subset of patients who may really benefit from an invasive and/or surgical approach.

NEUROLOGY 2

Activity normalization in SPECT with ^{123}I-ioflupane: removing the background without loosing the target

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Background and aim Activity normalization in single-photon emission tomography (SPECT) images is a well-established and key procedure, both in semi-quantitative and in statistical parametric mapping (SPM) analyses. An important step in activity normalization is the selection, using regions of interest (ROIs), of areas which can safely represent non-specific binding and free radioactivity. In ^{123}I-ioflupane SPECT imaging the use of occipital ROIs is consolidated in clinical practice, whereas in several studies the cerebellar areas are preferred. The aim of this study was to establish whether there exist significant differences between the two methods and, if so, to consider what the causes and the effects of these differences might be.
Materials and methods We studied the brain ^{123}I-ioflupane SPECT images of 70 adult patients (mean age: 68.77±9.32 years; 36 females and 34 males) referred to our institution with suspected Parkinson's disease (PD) between 2010 and 2011, defined as negative for PD both by visual and semi-quantitative analysis by an experienced operator and diagnosed with essential tremor by a neurologist at follow-up. All images were spatially normalized using a template created in our institution, then smoothed (6mm FWHM) using SPM8. Using MRIcro tools the ROIs were drawn in template areas corresponding, respectively, to the left and right occipital regions or to both cerebellar hemispheres. The ROI mean activity values were calculated for every patient and all images were activity normalized by both ROI types. Finally, comparative statistical analyses were performed in order to evaluate gender differences, corrected for age (only voxels with an uncorrected p-value <0.005 were considered statistically significant).
Results The analysis performed with cerebellar normalized images showed significantly higher ^{123}I-ioflupane uptake in the right and left striatum ($P_{corrected}$<0.001; 3494 voxels) in women, whereas the analysis performed with occipital normalized images, surprisingly, showed no significant differences between gender. To assess the possible causes of these dissimilar results, the cerebellar and occipital mean ROI activity values of our population were compared; this comparison showed a significantly (p<0.01) lower (about 40%) mean activity in occipital ROIs than in cerebellar ones. The differences between gender in mean ROI values were also assessed; this assessment showed no significant differences in cerebellar ROI mean activity but significantly (p=0.034) higher occipital ROI mean activity in females (males 64.24±14.17; females 73.04±19.76).
Conclusions The use of occipital rather than cerebellar ROIs for intensity normalization determines significant differences in statistical analysis results. Our data indicate that cerebellar mean ROI activity, compared to that of the occipital regions, is, though higher, more constant across genders, underlining a significant difference between male and female uptake of ^{123}I-ioflupane in the striatum. The use of these reference ROIs yields results which find confirmation in the current literature data. The difference between gender in occipital DaT concentration needs further studies, in the meantime the use of cerebellar ROIs seems to be recommendable for SPM analyses of DaTSCAN data.

Manual AC-PC reorientation of brain studies with [^{123}I]FP-CIT: effects on BasGan software analysis and clinical impact

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Background In recent years, SPECT imaging of the pre-synaptic dopaminergic system with [^{123}I]FP-CIT has become a very useful tool for studying many extrapyramidal syndromes. The uptake of the tracer in the basal ganglia can be evaluated using a semi-quantitative approach (based on measurement of activity in regions of interest – ROIs – positioned on the basal ganglia and the cerebral cortex) involving calculation of the caudate-to-occipital and putamen-to-occipital specific uptake ratios (SURs). The above-mentioned ROIs can be hand-drawn on the SPECT brain images; alternatively, they can be created by software for automatic segmentation of striatal SPECT studies. These software solutions, such as BasGan, are generally considered to provide reproducible and user-independent results.
Aim Our aim was to test the inter-observer reproducibility of BasGan software results in the analysis of striatal uptake of [^{123}I]FP-CIT, paying particular attention to the variability due to manual reorientation of the brain images on a plane parallel to the bicommissural line (AC-PC).
Materials and methods Data from 32 consecutive patients (18 M; mean age 70 ± 9 years), undergoing imaging with [^{123}I]FP-CIT for movement disorders, were considered in this study (128 SURs were calculated, i.e. four per patient, two as caudate/occipital ratios and two as putamen/occipital ratios). To this end, SPECT images of each patient were reconstructed and AC-PC reoriented by three different physicians and then analyzed with BasGan by each of them. SUR values obtained for each ROI, in each patient, with any reorientation, were defined as normal or pathological (as compared to SUR values obtained from a database of age-matched healthy subjects, taking 97% confidence interval lower limit as the cutoff).
Results In the AC-PC reorientation process we observed some significant variance among the physicians, the highest differences being found in the sagittal plane; these discrepancies impacted on the SUR software calculated values: the mean percent difference between operators was 6 ± 9% with a maximum difference, in the putamen, of 66.7%. As for the ROI analysis, in 7/32 patients (22%) at least one SUR value was classified differently (normal vs pathological) by at least one physician. In particular, we observed non-uniform classification of 8/128 SURs (6.2%). Unsurprisingly, this variability in SURs was most marked for uptake values close to the predicted cutoff of normality: 7/8 misclassified SURs were within 10% of the cutoff value. Had only the software-based results been taken into consideration, the final reports of three patients would have shown different conclusions (normal vs pathological) between physicians.
Discussion and conclusions The reproducibility of BasGan software results in the analysis of striatal uptake of [^{123}I]FP-CIT has already been assessed in the past. However, the problem of user-dependent reconstruction and AC-PC reorientation of the images to be submitted to the software has not yet been fully evaluated. In our study, we found that the inter-observer reproducibility of the results was good and consistent with previous findings, with a mean between-physician difference of 6% in the calculated SURs. This variability cannot be overlooked in the case of results close (within 10%) to the cutoff value for normality, as it can result in misclassification (normal/pathological) of the striatal structure. In this setting, the use of further aids in the AC-PC reorientation process, such as co-registration with a predefined reoriented template, must be considered, especially for borderline results.

Dopamine transporter availability in actively drinking alcoholics: preliminary results

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Aim Alcoholism may be considered a chronic disorder, characterized by craving, loss of control, tolerance and physical dependence. Among the several neurotransmitter systems involved in the neurobiology of alcohol dependence, dopaminergic pathways may play a crucial role, as suggested by animal studies**.** PET investigations showed a reduction in D2 receptor availability and a blunted dopamine release in the striatum of detoxified alcohol-dependent subjects. Contrasting results on dopamine transporter (DAT) availability have been reported in short- and long-term abstinent alcoholics by SPECT. We investigated DAT availability in actively drinking alcoholics using ^{123}I-FP-CIT SPECT.
Materials and methods We enrolled 10 patients (9 M, mean age: 50 ± 10 yrs) with a DSM-IV diagnosis of alcohol dependence and without a psychiatric axis I disorder. Mean duration of alcohol dependence was 18 yrs (± 13): 6/10 patients developed alcohol dependence after the age of 25 yrs and 7/10 were cigarette smokers. Each patient underwent a physical, psychiatric and neurological examination; routine laboratory and urine tests were performed. The Alcohol Dependence Scale (ADS) was used to assess severity of alcohol dependence; alcohol craving, including its obsessive and compulsive components, was evaluated using the Penn Alcohol Craving Scale (PACS) and Obsessive Compulsive Drinking Scale (OCDS). Anxiety and depression levels were evaluated by the State-Trait Anxiety Inventory (STAI) and Zung Depression Self-Rating Scale. The Timeline Followback (TLFB) was used to estimate daily alcohol drinking in the 4 weeks immediately prior to enrollment. The mean length of abstinence from the last drink to SPECT scan was 4.5 days. SPECT was carried out 3 hours after 148 MBq ^{123}I-FP-CIT intravenous injection. Specific to non-specific ^{123}I-FP-CIT binding ratios in the striatum, caudate nucleus and putamen were bilaterally calculated, based on 2D ROI analysis. The control group consisted of 14 healthy subjects (10 M, mean age: 47 ± 12 yrs).
Results In comparison with healthy subjects, alcoholics showed lower ^{123}I-FP-CIT binding ratios in the bilateral striatum and putamen (right striatum: -15%; left striatum: -16%; right putamen: -24%; left putamen: -23%; $p<0.05$, Mann-Whitney U test). An inverse correlation was found between the number of drinking days (as assessed by TLFB) and ^{123}I-FP-CIT binding ratios in the right striatum and bilateral caudate ($p<0.05$, Spearman's correlation analysis). The number of abstinence days (as assessed by TLFB) positively correlated with ^{123}I-FP-CIT binding ratios in the right striatum and bilateral caudate ($p<0.05$). Similarly, positive correlations were found between ^{123}I-FP-CIT binding ratios in the bilateral caudate and the number of days elapsing from the last drink to SPECT scan ($p<0.05$). The severity of alcohol craving (PACS score) was associated with lower DAT availability in the right caudate ($p < 0.05$). No correlations were found between ^{123}I-FP-CIT binding ratios and depression or anxiety levels (Zung SDS and STAI scores). The severity and duration of alcohol dependence did not correlate with ^{123}I-FP-CIT binding ratios in any of the regions.
Conclusions Our preliminary results showed decreased striatal DAT availability in actively drinking alcoholics, supporting the assumption of a hypofunctional dopaminergic system in alcohol-dependent subjects. These findings are in agreement with some previous neuroimaging and post-mortem autoradiography results and suggest that dopaminergic neurons could be a target for potential useful treatments of alcohol dependence.

The influence of dopaminergic striatal innervation on upper limb locomotor synergies

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Aim Upper limb locomotor synergies are a basic component of human gait. A reduced arm swing while walking is a clinical hallmark of Parkinson's disease (PD), suggesting the involvement of the basal ganglia in the control of locomotor automatism. The aim of this study was to investigate a putative role of dopamine and the striatum in locomotor upper limb automatism.
Methods We tested 13 consecutive subjects with idiopathic PD (six males; mean age: 64 years; disease duration mean: 5 years) and a control group (HC) of 10 neurologically intact adults (seven males; mean age: 64 years). Kinematics of body segments were measured during walking using an optoelectronic system, which computed the 3D coordinates of spherical markers attached on fixed bone landmarks. We calculated the range of motion (ROM) of absolute arm angle and arm swing asymmetry (ASA). The PD subjects and age-matched healthy subjects underwent ^{123}I-FP-CIT SPECT. Caudate and putamen binding uptake of both PD patients and healthy subjects were calculated using automated and operator-independent VOI analysis of the Basal Ganglia Matching Tool software. FP-CIT striatal uptake values were also used to calculate an asymmetry index (AI).
Results All patients showed a reduction of gait-associated arm movements. In comparison to HC, patients showed reduced DAT binding values in the putamen (PD, median: 2.3; HC, median: 4.9) and caudate nucleus (PD, median: 4.1; HC, median: 5.1), thus further confirming the clinical diagnosis of PD. The average AI value for the putamen of the PD patients was 30; all the HC subjects had a putamen AI score below 5 (putamen AI score average 2.1). All the PD subjects showed reduced ROM at one arm, and four bilaterally (ROM<18°). In PD patients, oscillations of the most affected side were significantly reduced compared to the contralateral side and to HC ($p<0.01$). Average ASA value was 29 for PD and 6 for HC. No statistically significant difference was found when comparing right and left arm ROM in HC. Arm range of motion while walking did not correlate with contralateral striatal dopaminergic innervation. The ASA and AI indices of both the caudate nucleus ($p<0.005$) and the putamen ($p<0.001$) were strongly correlated. This correlation proved to be statistically significant also when weighted for UPDRSrb and UPDRS-III scores.
Conclusions This study shows that the imbalance of dopaminergic striatal tone between the two hemispheres was predictive of the asymmetry of bilateral arm swing. These results suggest an active role of dopaminergic striatal innervation on the coordination of inter-arm locomotor synergies, rather than arm ROM amplitude per se.

The severity of cardiac sympathetic denervation is not related to presynaptic nigrostriatal degeneration in Parkinson's disease

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Aim The aim of our study was to investigate the relationship between myocardial sympathetic and nigrostriatal degeneration in patients affected by Parkinson's disease (PD) by means of both ^{123}I-MIBG scintigraphy and ^{123}I-FP-CIT SPECT.
Patients and methods The study involved 37 patients with a clinical diagnosis of PD [22 males and 15 females, mean age 62 years (±10); 15 Hoehn & Yahr (H&Y) stage 1, 8 stage 1.5, 7 stage 2 and 7 at stage 3]. All were first evaluated by means of ^{123}I-FP-CIT SPECT using a standard technique and then by ^{123}I-MIBG scintigraphy, performed 20(±3) days after the ^{123}I-FP-CIT SPECT scan. For ^{123}I-MIBG scintigraphy early (15 minutes) and delayed (4 hours) anterior chest images were acquired and the heart/mediastinum ratio (H/M ratio) was calculated. Linear regression and Spearman's correlation were used in order to assess a relationship between striatal ^{123}I- FP-CIT and cardiac ^{123}I-MIBG uptake.
Results We did not find statistically significant relationships between ^{123}I-MIBG cardiac and ^{123}I-FP-CIT striatal uptake in the caudate contralateral to the clinically more affected side either on early (r^2=0.03741, p=0.2514; r=0.2368, p=0.1582) or on delayed images (r^2=0.03741, p=0.2514; r=0.2368, p=0.1582), or in the contralateral putamen on early (r^2=0.003646, p=0.7226; r=0.1576, p=0.3517) or delayed images (r^2=0.001972, p=0.7941; r=0.2250, p=0.1806). Neither was any statistically significant relationship found at any level when considering the ipsilateral striatum (both caudate and putamen).
Conclusions The results of our study suggest that the cardiac sympathetic system and nigrostriatal system are differently affected in PD. In particular, in our series, the sympathetic neurodegeneration rate was not related to nigrostriatal degeneration rate as detected by means of ^{123}I-MIBG and ^{123}I- FP-CIT scintigraphy, respectively.

INFLAMMATION – INFECTION

Clinical impact of ^{99m}Tc-HMPAO autologous leukocyte SPECT/CT in the diagnostic workup of patients with suspected device related infections

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Background The use of cardiovascular implantable electronic devices (CIEDs, including permanent pacemakers, implantable cardioverter-defibrillators, cardiac resynchronization therapy devices) has increased significantly over the last decade due to growing evidence of improved quality of life and survival among certain groups of patients. However, the rate of associated complications, particularly infections, has increased disproportionately. Early recognition of CIED-linked infections and accurate quantification of disease burden are the two key elements for prompt treatment decision making.
Methods and results We evaluated, with ^{99m}Tc-HMPAO-WBC scintigraphy (including SPECT/CT acquisition), 63 consecutive patients in whom CIED infection was suspected on the basis of clinical and laboratory parameters, local signs of infection and/or abnormal echocardiographic findings. A total of 75 scans were performed to assess the ability of this functional imaging technique to identify the presence of CIED infection and to estimate disease burden. On the basis of the scintigraphy results, patients were treated with device extraction followed by antimicrobial therapy after microbiological confirmation of infection, antimicrobial therapy alone, or other disease-specific surgical procedures. In the latter cases a clinical follow-up of 12 months was performed and ^{99m}Tc-HMPAO-WBC scintigraphy was repeated at the end of the standard antimicrobial therapy. All patients underwent clinical examination, blood tests, urine analysis, blood culture, echocardiography (transthoracic TTE, transesophageal TEE, or both). CIED infections were finally diagnosed in 32/63, with microbiological confirmation after extraction in 23/32. In the remaining 9/32 cases the diagnosis was obtained through 12 months of clinical follow-up. ^{99m}Tc-HMPAO-WBC scintigraphy had high sensitivity (94%) for both diagnosis and localization of CIED infection. In the majority of the cases pocket infection was associated with involvement of the leads. The intracardiac portion of the lead(s) was the site most frequently involved in ^{99m}Tc-HMPAO-WBC uptake and it was also associated with the highest rate of complications: infectious endocarditis (18%) and/or septic embolism (47%). No false positive results were observed. False negative findings were encountered in 2 cases of CIED infection, with Candida spp. and Enterococcus spp, respectively. None of the patients with negative ^{99m}Tc-HMPAO-WBC scintigraphy, including 1/43 with positive blood culture, developed CIED infection during follow-up. Echocardiography also had high specificity (90%), but relatively low sensitivity (about 63%, increasing to 75% when including only patients with infections localized at the intracardiac portion of the leads). Application of the Dukes criteria resulted in 31% sensitivity for the "definite" category, increasing to 81%, when considering both the "definite" and the "possible" categories; in the latter instance, specificity was only 77%.
Conclusions Our results demonstrate the high accuracy of ^{99m}Tc-HMPAO-WBC SPECT/CT in patients with high clinical suspicion of CIED infection in defining the presence of infection, establishing the extent of device involvement, and detecting complications. Furthermore, ^{99m}Tc-HMPAO-WBC scintigraphy excluded the presence of device involvement during a febrile episode and sepsis, with 95% negative predictive value.

^{99m}Tc-HMPAO autologous leukocyte SPECT/CT in the preoperative workup of vascular prosthesis and abdominal aneurysmatic dilatation infections

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Background Vascular prosthesis infection (VPI) occurs in 1-6% of cases, with death rates ranging between 15 and 75% and a major amputation rate of up to 70%. The success of surgical intervention is closely dependent on early diagnosis. Radionuclide techniques are generally used to solve unclear situations, when CT sensitivity is low (i.e., low-grade infection, and infection occurring early after surgery).
Methods Between 2005 and 2011, 65 patients (58 men and 7 women, mean age 71±8 yrs; range 55-88 yrs) were referred for ^{99m}Tc-HMPAO-WBC scintigraphy to evaluate suspected VPI (n=55) or suspected infection of abdominal aneurysmatic dilatation (n=10). A total of 85 scans were performed: for diagnosis in 65 cases (55 as an emergency

examination, 10 for deferred evaluation), and for assessment of the efficacy of antimicrobial treatment in 20 cases. All patients underwent clinical examination, blood tests including WBC counts, C-reactive protein, erythrocyte sedimentation rate, acute phase proteins, and electrophoresis, urine analysis, blood culture, US and CT. Patients referred for a diagnostic scan were classified according to Fitzgerald. A final diagnosis of VPI was obtained in 47/55 patients with vascular prosthesis and in 2/10 with abdominal aneurysmatic dilatation through either microbiological confirmation (n=38/49) or clinical diagnosis (n=11/49, all patients not surgically treated because of major contraindications), with clinical follow-up of at least 12 months in all patients. In all patients without a microbiological diagnosis, ^{99m}Tc-HMPAO-WBC scintigraphy was repeated at the end of antibiotic treatment. Whole-body and spot planar images were obtained 30 minutes (early), and 2, 4-6 and 20-24 hours (delayed images) after reinfusion of 370-555 MBq of ^{99m}Tc-HMPAO-WBC. SPECT/CT of the region of interest was acquired in all patients at 2 and 6 hours and repeated at 24 hours in cases of negative or doubtful imaging at 6 hours (Hawkeye, GE Healthcare). Both CT-attenuation-corrected and non-corrected SPECT images were evaluated using the Xeleris software. Positive scans were categorized as follows: (a) isolated VPI; (b) isolated extra-VPI; (c) VPI and extra-VPI; (d) other infections. For the site-based analysis, results of the planar, stand-alone SPECT, and SPECT/CT images were compared. The patient-based performance of SPECT/CT was compared for the different clinical indications.

Results ^{99m}Tc-HMPAO-WBC scintigraphy was positive in all patients referred for a diagnostic scan, confirming VPI/aneurysmatic dilatation infection in 47/55; in 8 cases alternative causes of infection were identified. US suggested VPI in 14/47 patients, while CT was positive in 25/47. Therefore, combined radical surgical explantation and antimicrobial therapy was initiated in 36/47 patients, whereas in 11 cases conservative medical treatment alone was performed because of major contraindications. Perioperative mortality was 5.5%, mid-term mortality (within 1 month) was 12%, and long term-mortality was 27%, mainly unrelated to infection. Survival rates in patients treated with surgery+antimicrobial therapy were similar to those in patients treated with antimicrobial therapy alone (61% versus 63%), while infection eradication at 12 months was significantly higher when surgery was performed (83.3% versus 45.5%).

Conclusions In patients with high clinical suspicion of VPI and inconclusive US/CT, clinical decision making based on ^{99m}Tc-HMPAO-WBC SPECT/CT results is feasible. In view of the higher rate of infection eradication when surgery is performed, the possibility, in high-risk patients without vascular complications, of limiting surgical trauma to the site of ^{99m}Tc-HMPAO-WBC uptake should be explored.

Large vessel vasculitis: role of FDG PET/CT in disease activity evaluation

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Background ^{18}F-FDG PET/CT has been proposed as a useful tool for diagnosing and monitoring the activity of large vessel vasculitis (LVV), but its precise role remains debated. The objective of this study was to determine the value of PET-CT in the assessment of disease activity in LVV.

Methods A total of 215 PET/CT scans were performed in 78 patients with LVV (giant cell arteritis, Takayasu arteritis or idiopathic aortitis). PET/CT scans were reviewed by a nuclear medicine physician without knowledge of the clinical information. Vascular uptake was graded using a 4-point semi-quantitative scale where grade 0=no uptake, grade 1=less than liver uptake, grade 2=similar to liver uptake, and grade 3=higher than liver uptake. Visual analysis was performed on 14 vessel segments. PET/CT scans were considered negative if vascular FDG uptake was grade 0-1, moderately positive if vascular uptake was grade 2, and markedly positive if vascular uptake was grade 3 in at least one vessel. PET/CT findings were correlated with clinical indices including the Indian Takayasu Activity Score (ITAS) and Kerr/National Institute of Health (Kerr/NIH) index, serum acute-phase reactant (ESR, C-reactive protein [CRP]) levels, as well as interleukin-6 (IL-6) and the soluble IL-6 receptor (sIL-6R). ITAS, Kerr/NIH, ESR, CRP, IL-6 and sIL-6R values were obtained within 20 days of PET/CT scans.

Results 43% of 215 PET-CT scans were negative, 31% were moderately positive, and 26% were markedly positive. A significant correlation between the intensity of the uptake and both ESR and CRP levels was found. Significantly higher ESR values were observed in the patients with markedly positive PET/CT (49.4 $\pm$ 36.5 mm/1st h) compared with those with moderately positive (27$\pm$ 21 mm/1st h, p = 0.0001) and inactive scans (22.7 $\pm$ 15.9 mm/1st h, p=0.0001), respectively. CRP levels were 0.8$\pm$1.0 mg/dL in patients with inactive scans, 1.3$\pm$ 2.2 mg/dL in patients with moderately positive (p=0.001) and 3.0 $\pm$ 3.6 in patients with markedly positive scans (p = 0.0001). Significantly higher levels of IL-6 were found in patients with markedly positive scans (10.0 $\pm$ 8.9 pg/ml) compared to those with inactive scans (8.1$\pm$18.5 pg/ml, p=0.013). We found no association between sIL-6R levels and intensity of vascular FDG uptake. There was a significant association between the intensity of vascular FDG uptake and both ITAS and Kerr/NIH scores. Patients with markedly positive scans more frequently (50%) had active vasculitis according to the ITAS compared with those with moderately active (31.7%) and inactive scans (28.1%) (p=0.003). Likewise, vasculitis was judged to be active according to the Kerr/NIH index in 50% of patients with markedly positive scans, 22% of those with moderately positive scans, and 14.6% with inactive scans (p=0.0001).

Conclusions Our data show a strong association between vascular FDG uptake and clinical activity and traditional inflammatory markers. A weaker association was found between vascular FDG uptake and IL-6 levels. These findings suggest that PET/CT may be a useful tool for evaluating disease activity in patients with LVV.

The clinical value of ^{18}F-FDG PET/CT in the management of patients with suspected infection and fever of unknown origin

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Aim To evaluate the clinical impact of ^{18}F-FDG PET/CT on the diagnosis and management of selected patients with suspected infection and fever of unknown origin (FUO).

Materials and methods Thirty-eight patients (22 men, 16 women; age range: 21-85 years) with clinical and diagnostic suspicion of bone or vascular graft infection (n=27) or FUO (n=11) were studied by ^{18}F-FDG PET/CT and retrospectively evaluated. ^{18}F-FDG PET/CT find-

ings were confirmed by either clinical/imaging follow-up or microbiological/histological findings.
Results ^{18}F-FDG PET/CT was positive in 27/38 patients and correctly detected the localization and the extent of disease, both in adjacent and in distant sites, in 22/27 (81%) positive studies. In particular, it allowed the diagnosis of infection of either the axial or peripheral skeleton (n=6), infection of the aortic prosthesis (n=4), or infection limited to soft tissues (n=5), and thus resulted in optimization of the therapeutic strategy (antibiotic therapy or surgical intervention). In addition, ^{18}F-FDG PET/CT findings guided additional investigations (e.g. biopsy) or treatment planning in 7 patients with FUO, whose final diagnoses were: spondylodiscitis with extension to the psoas (n=1), spondyloarthritis (n=1), septic arthritis (n=1), thyroiditis (n=1), liver abscess (n=1), aortitis with a muscle abscess (n=1) and Hodgkin's lymphoma (n=1). In the remaining 5/27 (19%) cases, ^{18}F-FDG PET/CT was false positive and showed a peculiar linear ^{18}F-FDG uptake due to postoperative repair tissue in a recent sternotomy and foreign body aseptic reaction in vascular grafts, even years after surgery. ^{18}F-FDG PET/CT was negative in 11/38 cases and influenced the therapeutic management in 8/11 (73%) patients with doubtful morphological imaging. In particular, it could exclude the presence of spondylodiscitis (n=3) or infectious pseudoaneurysm (n=4), allowing reconstructive surgery, and it suggested the diagnosis of neurotoxoplasmosis in one HIV-positive patient with an intracranial mass lesion, suspected to be lymphoma on magnetic resonance scan. The remaining 3/11 (27%) negative patients had FUO and in these cases ^{18}F-FDG PET/CT did not contribute to a final diagnosis. In the whole population of 38 patients, ^{18}F-FDG PET/CT modified patient management in 23 (60%) cases.
Conclusions ^{18}F-FDG PET/CT is a valuable tool in the diagnosis of well selected cases of bone or vascular infection, especially those with doubtful morphological imaging, and in patients with FUO, allowing precise evaluation of both the localization and extension of disease foci, with a strong impact on patient management.

Comparison of organ kinetics of radiolabeled eosinophils, neutrophils and mixed granulocytes

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Background Lung uptake is often seen on early white blood cell (WBC) scans, and complete clearance is used as an *in vivo* quality control indicating WBC vitality. However, variable migration times can be observed in different patients.
Aim In this study we investigate the *in vivo* lung kinetics of ^{99m}Tc-HMPAO labeled mixed granulocytes, compared to that of pure eosinophils and pure neutrophils in human volunteers.
Methods For separate analysis of clearance of pure eosinophils and neutrophils, 100 ml of blood was obtained on two different occasions from 5 human volunteers and granulocytes were separated using Ficoll-Paquegradient centrifugation. Superparamagnetic particles, coupled to a monoclonal antibody against CD16 - a surface marker present in neutrophils but not eosinophils - were incubated with mixed granulocytes. The CliniMACS system (Miltenyibiotec, Bergisch-Gladbach, Germany; and Becton-Dickinson, Oxford, UK) was used to obtain highly purified (>93% pure) human blood eosinophils (negative selection) or neutrophils (>97%, positive selection). Four additional volunteers were injected with radiolabeled mixed granulocytes. Purified cells or mixed granulocytes were labelled with ^{99m}Tc-HMPAO (Ceretec, GE Healthcare) under aseptic cGMP conditions and 75-100 MBq of labeled cells were administered intravenously. Dynamic images of the lungs were acquired for the first 32 minutes after injection. Time-activity curves (TACs) were obtained on anterior and posterior projections and compared using appropriate statistical analysis.
Results Mean radiolabeling efficiency was variable, being 72%, 26% and 60% for pure eosinophils, pure neutrophils and mixed granulocytes, respectively. The kinetics of cells in the lungs had a bi-exponential character with a very fast first phase <5 min. The second phase revealed a significant difference for different cells: in particular, eosinophils cleared much faster than neutrophils (mean T1/2: 4.1 and 13.7 minutes for eosinophils and neutrophils, respectively, $p<0.009$). The kinetics of mixed granulocytes was slower (mean T1/2: 19.2 minutes). Separate analyses on blood, liver and spleen kinetics were also conducted.
Conclusions Different labeling efficiencies and kinetics were observed for neutrophil, eosinophil and mixed granulocytes. This implies that different WBC composition in the donor's blood may be responsible for variable degrees of uptake in the lungs, which need to be taken into account for the interpretation of WBC images.

RADIOPHARMACY

A new PET radiopharmaceutical with high affinity for amyloid fibrils

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Background ^{99m}Tc-aprotinin has been reported to accumulate in extrarenal amyloid deposits with high sensitivity and specificity.
Aim The aim of this work was to test the affinity for amyloid fibrils of a new PET aprotinin derivate.
Methods Recombinant aprotinin (rA) was conjugated with the intermediate chelator p-SCN-Bz-NOTA (N) to obtain the conjugate (AN). AN was purified by filtration on ultracel-PL membrane and labeled with ^{67}Ga chloride (ANGa). Quality control was performed using the HPLC method both before and after purification [R/T UV N 2x10-4M = 14.58 min., UV spectrum with max absorbance at 227 nm and at 275 nm (70% of the first one), R/T UV A 2x10-4M = 13.44 min., UV spectrum with max absorbance at 223 nm and at 275 nm (8% of the first one), R/T UV ANGa = 14 min., R/T ChA = 13.32 min., UV spectrum with max absorbance at 230 nm]. Molecular stability was controlled by HPLC analysis, also performed at different times (20, 30, 60, 240 min. and 12 and 24 h from labeling), with good results (93, 86, 83, 61, 48, 46%). ANGa was used to asses the fibrillar binding assay: 7.26 μg/1 mL of fibrils, washed and spinned 3 times at 12000 rpm for 30 min at 25 °C, adjusted to 1 mL and separated in five 100 μL batchs HSA 5% coated (726 μg). Increasing amounts of ANGa (1 nmol, 4 nmol, 8 nmol, 12 nmol and 16 nmol) and increasing amounts of water (190, 160, 120, 80, 40 μL) were added to every sample up to a total volume of 300 μL. The same amounts of ANGa and water up to a 300 μL total volume were used as blank. After 1 h at RT incubation each sample was counted in a well scintillator, before and after washing (12000 rcp per 10 min). The non-specific binding was subtracted. For competition experiments increasing amounts of cold rA (35 – 280 nmol) were added to 1 mg fibril samples labeled with ANGa (70 nmol).
Results The synthesis reaction gave a yield of approximately 80%. Gallium labeling yield ranged from 73 to 86% and the compound was stable *in vitro* for at least 48 h. Scatchard analysis of the binding affin-

ity revealed a Kd of 86.62 nmol. Competition binding tests showed a 50% displacement at 129 nmol.
Conclusions The aprotinin affinity for amyloid fibrils is not affected by the rapid (15 min at RT) and good labeling of recombinant aprotinin with ^{67}Ga after p-SCN-Bz-NOTA chelation, with a Kd comparable to that we previously reported for technetium-labeled A. Therefore ANGa may be considered a new PET radiopharmaceutical with high affinity for amyloid deposits.

Exploiting the high reactivity of [^{11}C]methyl-triflate for the synthesis optimization of the β-amyloid imaging tracer N-methyl-[^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole, [^{11}C]PIB

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Aim [^{11}C]Methyl-triflate has been shown to be a highly reactive alternative to [^{11}C]methyl-iodide in the synthesis of radioligands for positron emission tomography (PET). The aim of this work was to set up a high-yield radiosynthesis of [^{11}C] methyl-triflate and optimize [^{11}C] PIB radiolabeling with this methylating agent.
Materials and methods No carrier added [$^{11}CO_2$] was produced via the ^{14}N(p,a)^{11}C reaction using an IBA Cyclone 18/9 cyclotron (Louven la Neuve, Belgium) and transferred into a Ge Healthcare Tracerlab-FX_C-Pro module remotely controlled via Tracerlab FX -SW (software version 2.2.2.0). [^{11}C]CO_2 was trapped on a molecular sieve and, by using the gas phase reaction, converted to [^{11}C]CH_4 in the presence of Ni catalyst and hydrogen at 350°C. Allowing recirculation for 300s, [^{11}C] CH_4 was reacted with elemental iodine (contained in a quartz loop) at 720°C to produce [^{11}C]CH_3I. [^{11}C]CH_3I was then trapped on line in a Porapak Q small peek column at room temperature using a stream of helium and finally released by heating the column to 190°C. [^{11}C]CH_3I was converted into [^{11}C] methyl-triflate by on-line passage of helium flow through a heated column (200°C), containing about 300 mg of silver triflate impregnated into graphitized carbon. [^{11}C] methyl-triflate was bubbled into the reactor of the automatic remotely controlled synthesizer module, filled with 1 mg of precursor 6-OH-BTA-O [2-(4'-aminophenyl)-6-hydroxybenzothiazole] dissolved in 500 ml of 2-butanone kept at 13°C. The reactor was then heated to 75°C for 2 min. After cooling down to 25°C the reaction mixture was diluted with 1 ml of HPLC eluent and then transferred to a semi-preparative radio-HPLC system, equipped with a Sykam S1021 pump (Fuerstenfeldbruck, Germany), a reverse-phase column (Luna C18 100A, 250x10.0 mm, 10 m Phenomenex), an ultraviolet detector (UV 280 nm), and a radioactivity flow detector. Elution was carried out with absolute ethanol/tri-sodium citrate dihydrate 0.01 M (40/60, v/v) as mobile phase at 4 ml/min flow rate. To avoid autoradiolysis of the compound, 0.1% of vitamin C was added to the mobile phase. [^{11}C]PIB was collected from semi-preparative column and sterilized by a 0.22mm filter (Millex-GP PES Millipore) into a sterile vial. The purity of the labeled compound [^{11}C] PIB was analyzed using an Eclipse Plus C18 reverse-phase column, 250x4.6 mm, 5 m (Agilent, USA) connected to an ultraviolet detector (UV 350 nm) and a radioactivity flow detector. The mobile phase for HPLC was CH_3CN/tri-sodium citrate dihydrate 0.01 M (50/50, v/v) at a 1 ml/min flow rate.
Results and conclusions Based on [^{11}C] methyl-triflate activity the radiochemical yield of [^{11}C]PIB was 43% corrected for decay. Radiochemical purity was > 98% as determined by radio HPLC. The tracer solution was sterile and apyrogenic. The specific activity was 1± 0.2Ci/mmol. The results of the present study indicate the advantages of [^{11}C] methyl-triflate in N-methylation reactions, which important for reliable routine production. These advantages are: a higher radiochemical yield, a shorter synthesis time, a higher specific radioactivity, a lower precursor amount and simplified automation. The promising beta-amyloid PET imaging agent [^{11}C]PIB was radiolabeled in one step using [^{11}C] methyl-triflate. No protection of the 6-hydroxygroup was required, greatly simplifying the synthesis method.

PEGylated *N*-methyl-*S*-methyl dithiocarbazate as a new reagent for the high-yield preparation of Nitrido ^{99m}Tc and ^{188}Re radiopharmaceuticals

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Aim The current availability of efficient methods for the high-yield production of ^{99m}Tc and ^{188}Re-compounds containing the $[M(N)]^{2+}$ (M= ^{99m}Tc, ^{188}Re) group at no-carrier-added (NCA) level has stimulated interest in the preparation of new ^{99m}Tc and ^{188}Re radiopharmaceuticals for diagnostic and therapeutic applications. $[M{\equiv}N]^{2+}$ core (M = ^{99m}Tc and ^{188}Re) exhibits redox inertness and high stability over a wide range of pH values, a fact that makes it an interesting candidate for nuclear medicine applications. Polyethyleneglycol (PEG) is the most successfully used polymer in pharmaceutical science for conjugation to organic molecules and small drugs, because of its unique characteristics, such as absence of immunogenicity and toxicity and high water solubility. A novel PEG derivative nitrido nitrogen atom donor for the preparation of ^{99m}Tc and ^{188}Re radiopharmaceuticals containing a metal-nitrogen multiple bond is presented.
Materials and methods HO_2C-PEG_{600}-DTCZ was obtained by conjugation of *N*-methyl-*S*-methyl dithiocarbazate [H_2N-N(CH_3)-C(=S)SCH_3, HDTCZ] with polyethylene glycol 600 (PEG_{600}). Asymmetrical heterocomplexes of the type $[M(N)(PNP)(B)]^{0/+}$ (M = ^{99m}Tc, ^{188}Re; PNP = diphosphine ligands, B = bidentate ligand) were prepared in high yield using the newly designed nitride nitrogen atom donor HO_2C-PEG_{600}-DTCZ.
Results A two-step procedure was applied for preparing the above symmetrical and asymmetrical complexes. The first step involved the preliminary formation of a mixture of nitride Tc-99m or Re-188 precursors, which contained the $[M{\equiv}N]^{2+}$ core, through reduction of generator-eluted ^{99m}Tc-pertechnetate or ^{188}Re-perrhenate with thin (II) chloride in the presence of HO_2C-PEG_{600}-DTCZ. In the second step, the intermediate mixture was converted into the final mixed asymmetrical complex by the simultaneous addition of diphosphine ligand and the suitable bidentate ligand B. Evaluation of stability of ^{99m}Tc and ^{188}Re-complexes in serum and towards transchelation with GSH and cysteine revealed no significant change of radiochemical purity (RCP) after 2 hours of incubation at 37 °C under different experimental conditions. Biodistribution studies in rats of the hitherto unreported $[^{99m}Tc(N)(PNP_3)DTCZ]^+$ and $[^{99m}Tc(N)(PNP_5)DTCZ]^+$ complexes showed that they selectively localize in the myocardium of rats with favorable heart-to lung and heart-to-liver uptake ratios. In particular, the heart-to lung and heart-to-liver uptake ratios dramatically increased in the interval between 60 and 120 minutes post injection.
Conclusions In this work we have described the rationale of the design of a new nitride nitrogen atom donor for the efficient preparation of technetium and rhenium nitrido radiopharmaceuticals. The polymeric HO_2C-PEG_{600}-DTCZ derivative was successfully synthesized and tested in the preparation of well-characterized categories of asymmetrical nitrido complexes, $[M(N)(PNP)(B)]^{0/+}$. PEGylated DTCZ did

not lose the ability to yield N^{3-} groups, but made it possible to obtain nitride ^{99m}Tc and ^{188}Re radiopharmaceuticals at higher specific activity as compared to the previous HDTCZ-based procedure. Moreover, the higher water solubility (140 mg cm^{-3}) of HO_2C-PEG_{600}-DTCZ paves way for its use in lyophilized kit formulations. Hence, the combination of the favorable chemical and biological properties of HO_2C-PEG_{600}-DTCZ might give this novel compound an important role for the development of new ^{99m}Tc and ^{188}Re-nitrido radiopharmaceuticals.

Practical experience in optimization of ^{64}Cu specific activity

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High specific activity and the absence of metallic contaminants in the labeling solution are critical parameters defining ^{64}Cu product quality. In most cases, and this applies to most known ^{64}Cu-labeled radiopharmaceuticals, other divalent transition metal cations can interfere or compete with the copper for labeling the limited amount of chelator available. The exact specific activity requirements will depend on the specific application, but a substechiometric labeling condition will always be necessary in order to obtain high labeling yields. The maximum theoretical specific activity of ^{64}Cu is 9.4 TBq/μMol (254 Ci/μMol). However this theoretical value is not achievable in practice, due to ubiquitous presence of inactive copper, which may leak into the production process. Possible sources of metal contamination are: the original ^{64}Ni target material and reagents for ^{64}Ni dissolution, the plating bath and purification assembly, glassware, water, ion exchange resin, and the degrader in front of the target, not to mention the target download system and the container for transportation. For nearly three years we performed ^{64}Cu purification and synthesis using an automatic device, largely based on standard Modular Lab components (Eckert & Ziegler). In the preparation phase of each process, all glassware and tools were washed with Alconox®, then with 0.5 M HNO_3 and 18 MΩ-cm water. Only ultra-pure reagents, with metal traces in the ppm range or lower, were used for the preparation of the target material and the radiochemical separation process. The solid target is made of a gold backing (32 mm diameter), on which about 200 mg of ^{64}Ni are electrodeposited using a Pt electrode. Irradiation is performed using a PETtrace cyclotron, typically for 180 min at 25 mA.
The specific activity of ^{64}Cu was experimentally assessed via titration of $^{64}Cu(OAc)_2$ with TETA. The irradiated ^{64}Ni is dissolved in 4 mL of HCl 6N at 90 °C, and then eluted through a 20x0.8 cm Bio-Rad AG1-X8 anion exchange column. After ^{64}Ni recovery (45 mL HCl 6N), the column is dried and the ^{64}Cu fraction is eluted with 0.1N HCl. In a typical experiment 50-150μCi of ^{64}Cu were reacted with various concentrations of TETA solution (10^{-3} mM - 10^{-9}mM) for 1h at 35 °C. Samples were spotted on silica plate and developed using 1:1 MeOH:10% NH_4OAc as mobile phase. Complexation (^{64}Cu-TETA) was monitored by radio TLC scanner. The amount of TETA which binds 100% of the copper-64 was assumed to be equal to the concentration of Cu(II) present.
Typical saturation yield in our production cycles was in the range of 40-70 mCi/μA, depending on irradiation conditions, while the recovery of ^{64}Ni was steadily better than 98%. Radionuclidic purity of ^{64}Cu is greater than 99.999% at 12h from the end of bombardment. Consistently adopting high purity materials, improving the glassware and module cleaning procedures, and using the same AG1-X8 resin for different separation runs, we were able to gradually improve the specific activity of produced ^{64}Cu from an initial 2 Ci/μmol to the final result of 34 Ci/μmol.

The automated process developed at our institution for production and purification provides ^{64}Cu with high yield and radionuclidic purity. The state-of-the-art level of specific activity of the final product, makes it perfectly suitable for labeling ^{64}Cu radiopharmaceuticals like antibodies, peptides and nanoparticles.

Suppression of side products formed during ^{68}Ga-bioconjugate labeling using radical scavengers

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Background The labeling of DOTA bioconjugates, such as peptides, vitamins or small molecules, with ^{68}Ga has become, in recent years, one of the most interesting fields of application in radiochemistry. The most widely used 68-Gallium-labeled probes are somatostatin analogs such as DOTATOC/TATE or NOC which have also acquired considerable importance in clinical practice. Even though these probes are widespread, many centers experienced the presence of 68-Ga-labeled side products in ^{68}Ga-DOTATOC/TATE/NOC preparations. This occurred to such a degree that the draft ^{68}Ga-DOTATOC monographs on European Pharmacopeia require only a > 91% radiochemical purity (RCP) checked by HPLC. The formation of ^{68}Ga side products appears to be dependent to radiolysis or oxidation processes.
Aim In the present study we assessed the effect of varying radical scavengers and antioxidants, namely selenomethionine, ascorbic acid and EtOH, on the RCP and radiochemical yield (RCY) of three ^{68}Ga-labeled bioconjugates, the aim being to suppress the presence of radiochemical impurities.
Materials and methods Three ^{68}Ga-labeled radiopharmaceuticals, namely DOTATATE, DOTA-AMBA and DOTA-Biocytin, were prepared using an automatic Modular Lab Synthesizer (Eckert & Ziegler) following the fractionating of the eluate according to previously described purification methods. The fraction containing about 80% of the ^{68}Ga was directed to the reactor and reacted with the appropriate amount of bioconjugates under the best conditions in terms of pH (3-4), time and temperature. After the reaction the crude solutions were purified passing through a plus C-18 cartridge and the labeled products were eluted with 2 ml of a 50% EtOH solution. The RCY and RCP of traditional preparations were compared to those obtained by adding varying amount of selenomethionine, ascorbic acid solutions (25, 50, 250 nmol) or EtOH (50, 100, 200 microl) to the reactor before labeling.
Results ^{68}Ga-DOTATATE: both ascorbic acid and selenomethionine solutions had a strong impact on the improvement of the RCP (from 93±2% to 99±1%) although at different amounts. Conversely, the addition of EtOH had a negligible effect on RCP. None of the three additives influenced the original RCY, which was 65±2%. ^{68}Ga-Biocytin: all the additives significantly contributed to improving the RCP (from 95±1% to 98±1%), but while ascorbic acid and selenomethionine did not influence the RCY (67±1%), the addition of EtOH decreased it greatly (by up to 7% when 200 microl were added). ^{68}Ga-DOTA-AMBA: the behaviour was similar to that found for ^{68}Ga-DOTATATE – ascorbic acid and selenomethionine improved the RCP (from 90±2% to 98±1%) while EtOH did not affect the RCP. RCY was only mildly influenced by EtOH while for the two other additives no notable differences were found (RCY remained 62±2%)
Conclusions Both ascorbic acid and selenomethionine solutions act as radical scavengers/antioxidants in the preparation of ^{68}Ga-labeled radiopharmaceuticals avoiding the formation of side products. Due to the suitability of ascorbic acid for human use we selected this additive as the best candidate to be employed in clinical preparations. The results obtained are of interest mainly for ^{68}Ga-DOTATATE preparations, given that this radiotracer is used in a number of nuclear medicine facilities.

PHYSICS AND INSTRUMENTATION

Assessment of the feasibility of producing ^{99m}Tc with a 16.5 MeV biomedical cyclotron using the TALYS nuclear reaction program and FLUKA code

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Aim ^{99m}Tc ($t_{1/2}$ = 6.02 h), now the most widely used radioisotope for diagnostic nuclear medicine, is mainly obtained from the decay of its parent ^{99}Mo ($t_{1/2}$ = 66 h). The recent worldwide shortage of reactor-produced ^{99}Mo has stimulated studies on the large-scale cyclotron production of ^{99m}Tc via the ^{100}Mo(p,2n)^{99m}Tc reaction, whose cross-section starts at about 8 MeV, peaks at 16 MeV and drops around 24 MeV. In this work we investigated the feasibility of producing ^{99m}Tc through a 16.5 MeV GE PETtrace cyclotron.
Materials and methods The validated TALYS nuclear reaction program was used to evaluate direct ^{99m}Tc production cross-sections on ^{100}Mo and ^{98}Mo targets in the [1÷30] MeV energy range and the corresponding ^{99g}Tc/^{99m}Tc isomeric ratios with 1 MeV energy bin; other molybdenum isotopes present in available enriched ^{100}Mo targets were investigated to assess production of impurities. The SRIM nuclear code was used to obtain proton stopping powers. The expected activities were evaluated for (1÷3) h irradiations at a current of 50 μA and for (100÷300) μm target thicknesses. These results were compared with MonteCarlo FLUKA code simulations performed considering a 97.46% enriched ^{100}Mo target; in the model, an elliptically shaped proton beam was degraded by a 25 μm Havar foil before entering a 32-mm diameter disk with a thickness (target+backing) not exceeding 2 mm, according to the design of the solid target station operational at our institution. The Russian roulette biasing technique was used to reduce variance and improve simulation results for thin targets; the current FLUKA isomer patching method was used, meaning 50% splitting between ground state and isomer. In order to overcome this limitation, simulations were then performed with no patching and the number of produced nuclei was scaled to TALYS isomeric ratios.
Results TALYS cross sections show good agreement with Takacs et al. and Scholten et al., but are inferior to the results of Lagunas-Solar and Levkovskij. According to this study, a 150 μm (16.03 13.3 MeV) enriched ^{100}Mo target, practically achievable with electrodeposition techniques, allows the production of clinically relevant amounts of ^{99m}Tc while keeping impurities at a reasonably low level. The TALYS average ^{99m}Tc isomeric ratio in this energy range was (20.9±1.1)%, in agreement with Scholten et al. and similar to a generator eluted at 24-h frequency with a 5% retention; the saturation yield for 2 hours' irradiation was (1.11±0.06) GBq/μA. FLUKA simulations with 50% isomer splitting provided a yield of (2.680±0.008) GBq/μA, while scaling of the number of produced nuclei lowered the result to (0.99±0.05) GBq/μA. The isotopic impurities produced were ^{100}Tc ($t_{1/2}$ = 15.8 s), ^{97m}Tc ($t_{1/2}$ = 90.1 h) and smaller quantities of ^{99g}Tc, ^{98}Tc and ^{97g}Tc (half-lives longer than 10^5 y). The radionuclidic purity of ^{99m}Tc was found to be >99.6 % at 2 hours after the end of bombardment.
Conclusions The optimal irradiation condition for the production of ^{99m}Tc with a standard 16.5 MeV biomedical cyclotron was studied with an analytical code and MonteCarlo simulations. ^{99m}Tc isomeric ratios provided by TALYS were exploited to overcome limitations of FLUKA due to the spin-parity independence of the evaporation model adopted in the code. These encouraging results suggest that this may be a feasible, relatively low-cost and large-scale alternative to generator-based production. Experimental tests are currently on going.

Quantification of the neoplastic volume in PET imaging for follow-up after treatment

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Aim PET with the glucose analog ^{18}F-FDG is commonly used to monitor tumor response in patients undergoing treatment. A new software program for quantification of the neoplastic volume in PET imaging was developed. This software implements the RIThM algorithm (recovering iterative thresholding method), proposed by Pacilio et al (Med Phys 2011;38:3050-61), on two PET scanners located at the Istituto Europeo di Oncologia. In this work, preliminary results on clinical images are presented.
Materials and methods This method requires calibration of the experimental imaging system. The validation of the method was initially carried out on test objects. The software was implemented in Matlab (Mathworks, Natwick, USA) and compiled to a stand-alone application. The graphical user interface is a user-friendly application that is now under clinical evaluation. The software allows graphical display of the 2D and 3D segmentation of the VOI (volume of interest), while also providing the volume of the lesion, the optimal threshold for the segmentation (also useful in the planning phase of radiotherapy treatments), and the contrast value. The images of 15 patients were analyzed to test the performance in clinical settings. The volumes of interest (secondary spleens, lymph nodes, and urinary bladders) were segmented on the CT images. The agreement between CT volumetric estimates and - RIThM results on PET images was statistically analyzed, using linear regression fit and Bland-Altman plots with ±95% confidence interval (CI).
Results The accuracy of volume determination for the test objects was within ±10% for most volumes in the range 1-98 mL. In the patients' images, a good correlation (R^2=0.928) was obtained between volumes segmented on CT and PET images by RIThM. Moreover, no significant bias was evidenced by the slope of linear regression (slope=1.04). This was also confirmed by the Bland-Altman plot: differences were within the ±95% CI, and the mean difference (bias line) was about 1 mL (close to zero).
Conclusions The analysis of the test objects and the preliminary results on clinical images demonstrate the robustness and accuracy of the method. A wider variety of cases is under analysis to confirm these results and further investigate the potential of the method. In addition, the ease of use of the software and the speed with which it produces data for the quantification of neoplastic volume make it a powerful tool to support the clinical diagnosis.

BTV estimation: a multi-center study of the robustness and the reliability of an adaptive thresholding method incorporating PET reconstruction parameters

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The robustness and reliability of an adaptive thresholding algorithm (ATA) incorporating PET reconstruction parameters were assessed in eleven PET/CT scanners.

Measurements were performed with the NEMA IEC Body Phantom. The background and the 9 spheres (internal diameters: 6.5;8.1;10;13;17;22;28;37;57.4 mm) were filled with different activity concentrations of ^{18}F-FDG to obtain nine different target-to-background ratios (TB: 2.5;4;8;16;25;35;47;55;70) and imaged with different emission scan durations (ESD: 2,3,4,5 minutes) in separate acquisition sessions on 11 PET/CT scanners (n.2 Discovery 600, n.2 Discovery ST, n.1 Discovery STE, n.1 Biograph HI-REZ, n.1 Biograph TRUEV, n.1 Gemini XL and n.1 Gemini TF). Images were reconstructed with clinical protocols (2D-OSEM, 3D-OSEM, 3D-LOR, TF-MLEM) varying the number of iterations (IT, from 14 to 108) and the post-reconstruction smoothing (FWHM, from 4 to 11 mm). Thresholds (TSs) were determined as a percentage of the maximum intensity in the cross-sectional area of the spheres. To find the TS value that yielded an area (A) best matching the true value, the cross sections were auto-contoured in the attenuation-corrected slices varying TS in steps of 1%, until A differed by less than 10mm^2 versus its known physical value.

For each scanner, the relationship between the best threshold that provides the most accurate cross-sectional area of the spheres and the variables A, TB and FWHM, was established using multiple linear regression methods for each combination of EM-equivalent iteration number and ESD, using the model:

$TS=B_0+B_1\ A(mm^2)+B_2\ (1\text{-}1/TB)+\ B_3\ FWHM\ (mm)+E$

where B_0, B_1, B_2 and B_3 are the regression coefficients that need to be estimated and E is the error term. The reliability of the regression models was assessed through split-sample analysis and was expressed by using the shrinkage on cross-validation coefficients R^2-R^2*.

ESD and IT of the reconstruction algorithm were not significant predictors of TS. For sphere A>133mm^2, which is in the range of clinically relevant volumes (V>1ml), the goodness of the model fit, assessed by the coefficient of determination R^2, was high (0.74-0.92). The most relevant variable for TS prediction was always TB with a partial R^2 accounting for between 74% and 91% of TS variability. For all scanners, except the Geminis, FWHM was an independent predictor of TS. Last came lesion size, which played an independent role only in the Discovery 690 and in the Geminis.

Significant differences were observed between scanners of different models, while no significant differences were detected between different scanners of the same model.

The shrinkage on cross-validation was small and indicative of excellent reliability of model estimation. The incorporation of FWHM in ATA for BTV estimation makes it possible to obtain a robust and reliable method that can be applied to a variety of different scanners by different vendors, without the need for individual calibration of each scanner at each site.

Correlation between standardized uptake values (SUV) and influx constant (Ki) calculated using the non-linear regression method in patients with lung cancer

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Background and aim The most common method for estimating the ^{18}F-FDG uptake is the standardized uptake value (SUV), a semi-quantitative dimensionless parameter which is easy to calculate. However, because it provides only an estimation of glucose consumption, it is considered a "surrogate" of the metabolic rate of glucose (MRglu). SUV is affected by several technical and methodological problems and many normalization schemes, including body weight (SUVbw), body surface area (SUVbsa) and lean body mass (SUVlbm), have been proposed to improve its accuracy. The influx constant (Ki) is used to calculate the MRglu in ^{18}F-FDG PET studies. Non-linear regression (NLR) is considered the best method for calculating Ki, as it combines -k1, k2, and k3, the rate constants of the compartmental model. NLR is not routinely applied because it is complex and time-consuming and, consequently, Ki and MRglu are not frequently used in practice. The aim of this study was: to correlate SUVbw, SUVbsa and SUVlbm with the Ki values calculated using the NLR method in patients with lung cancer, to verify whether it is possible to derive Ki from SUV.

Materials and methods Twenty-one patients (13 males, mean age 69.9±8.85years) with lung cancer underwent dynamic and whole-body ^{18}F-FDG PET-CT for staging. Thorax dynamic acquisition, lasting 60 minutes, was performed using 25 frames: 9 frames of 5 seconds each, 1 frame of 15 seconds, 4 frames of 60 seconds each, and 11 frames of 300 seconds each. Images were analyzed drawing two ROIs including the five hottest pixels: over the tumor (tissue response) in the last frame; over the descending aorta (input function) in the first 30 seconds summed frames. The ROIs were superimposed on all frames and time-activity-curves were generated. We took into account the following parameters: SUVbw, SUVbsa, SUVlbm at 45 and 55 minutes, and Ki obtained using the NLR method. The Pearson and Spearman correlation tests were used for statistical analysis.

Results At 45 minutes, we found the following mean values (±SD) for SUVbw, SUVbsa, and SUVlbm: 6.64±3.34, 1.64±0.82, and 5.56±2.95, respectively. At 55 minutes, we found the following mean values (±SD) for SUVbw, SUVbsa, and SUVlbm: 8±3.76, 1.98±0.94, and 6.76±3.42, respectively. The correlation coefficients between SUV at 45 minutes and Ki were the following: for SUVbw r=0.939 and rho= 0.917; for SUVbsa r=0.964 and rho= 0.939; for SUVblm r=0.917 and rho= 0.91. The correlation coefficients between SUV at 55 minutes and Ki were the following: for SUVbw r=0.945 and rho= 0.93; for SUVbsa r=0.967 and rho= 0.946; for SUVblm r=0.907 and rho= 0.926. Due to the high correlation between SUVbsa and Ki, we derived Ki from the linear regression equation: Ki= 0.0025 + 0.0207*SUVbsa. A very high correlation (r=0.965) between MRglu calculated using Ki derived from the linear regression equation (5.04±2.48ml/min/100gr) and MRglu calculated using Ki derived from the NLR (4.73±2.58ml/min/100gr) was found (lumped constant=1).

Conclusions In our patients, SUVbsa measured at 55 minutes of the dynamic ^{18}F-FDG PET-CT provided the best correlation with Ki calculated using the NLR. Due to this high correlation, it is possible, in clinical practice, to derive Ki (and consequently MRglu) from SUV values normalized for body surface area using a simple linear regression equation. However, it is also important to underline that all procedural aspects (quality control, acquisition parameters, injected activity,

blood glucose level, etc.) have to be rigorously checked to obtain a robust quantification.

Gated reconstruction in ^{18}F-FDG PET/CT quantitative imaging: how many respiratory phases?

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Aim To identify the optimal number of breathing phases in respiratory-gated PET/CT (4D-PET/CT) of lesions that move with respiration.
Methods Fifteen patients with lung tumors who underwent ^{18}F-FDG PET/CT were studied with a 4D-PET/CT additional acquisition after a whole-body scan. Patients were selected among the group that showed respiratory-induced tumor motion greater than 5 mm. 4D-PET/CT was performed with a Philips Gemini BigBore scanner capable of time-of-flight reconstruction, using the Varian RPM gating system. Administration and acquisition parameters were 3.0 MBq/kg ^{18}F-FDG, 2 min/bed, retrospective-mode for both PET and CT modalities. Patients were instructed to breathe as regularly as possible. Data were reconstructed in 1 (no sorting), 2, 3, 4, 5, 6, 7, 8, 9 and 10 breathing phases. SUVmax values within the lesion were studied as a function of the number of phases in phase(0%) (max expiration). Lesion volumes were also obtained by three different methods: (a) fixed SUV=2.2 threshold, (b) 40% of SUVmax isocontour, and (c) gradient-based method. The volumes were also studied as a function of the number of phases in phase (0%).
Results The observed maximum range of motion was 5.5 mm (L-R), 16.5 mm (A-P) and 22.2 mm (S-I). SUVmax was on average 67.4% higher in the gated acquisition (10 phases) compared to the non-gated case (range 13.1%-328.3%). When comparing reconstructions in 4 and 10 phases, the average increase in SUVmax was reduced to 13.3% (range 2.3%-31.2%). Corresponding figures for 6 to 10-phase comparison were 6.8% and range 0.0%-23.1%. In general, volumes estimated by the fixed-threshold method increased with increasing phase number, volumes obtained with the percentage method decreased, and volumes obtained with the gradient-based method did not show a significant trend. On average, volumes calculated in the 10-phase ph(0) image by method (a) were 8.9% higher than volumes obtained by method (b), while the static acquisition (no gating) method (a) gave volumes 20% smaller than method (b), on average.
Conclusions 4D-PET/CT offers a clear advantage in ^{18}F-FDG SUV estimation of tumors that move with respiration. The balance between acquisition/reconstruction time, signal-to-noise ratio and SUV estimation accuracy seems to be achievable splitting the respiratory cycle into 4 to 6 phases, depending on lesion location. The same observation holds for lesion volumes, however further research is needed to determine the optimal segmentation method. Gradient-based methods are less sensitive to the number of phases for volume estimation, however further study is necessary to fine-tune and validate their results.

RADIONUCLIDE THERAPY AND DOSIMETRY 1

Cross-institutional comparison of estimated activities required to treat hyperthyroidism

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Background and aim Hyperthyroid patients are treated with ^{131}I for decades. However, the activity to be administered in patients with small pool syndrome is still debated given the risk of irradiation of healthy tissues. The aim of this study was to evaluate Italian and European guidelines, as well as the ICRP approach, on estimating the ^{131}I activity required for patients with hyperthyroidism and a strong suspicion of small pool syndrome.
Materials and methods Forty consecutive patients, 28 with Graves' disease and 12 with autonomous thyroid nodule (ATN), referred to our center for radioiodine treatment of the hyperthyroidism, were included in this study. All patients underwent the radioiodine uptake test (RIU) to evaluate iodine metabolism. Maximum uptake, effective half-life and residence time were estimated from RIU data. In order to estimate residence time for each patient, the iodine system was studied according to a bicompartimental model and fitted with the equation: $U_{pt(t)}/U_{ca(t=0)}=(e^{-a*t}-e^{-b*t})*(U*a)/(b-a)$; where $U_{pt(t)}/U_{ca(t=0)}$ is the patient's thyroid uptake at time t normalized for capsule uptake at time 0; U, a and b were estimated by the function fit. Activity was computed according to AIMN and EANM guideline algorithms as well as according to the ICRP53 approach. OLINDA/EXM (MIRD committee) results were used as gold standard.
Results According to the AIMN guideline algorithm, the activities to be administered were significantly higher both in Graves' disease ($p<0.0001$) and in ATN ($p=0.008$). The mean differences between the activity calculated using OLINDA and the AIMN algorithm were 20% and 42% in Graves' disease and in ATN respectively. According to the EANM guideline algorithm, the mean activities to be administered were 3% higher both in Graves' disease ($p=0.001$) and in ATN ($p=0.046$). According to the ICRP 53 approach, the mean activities to be administered were significantly lower both in Graves' disease ($p=0.017$) and in ATN ($p=0.014$). Mean differences between OLINDA and the ICRP 53 approach were 33% and 17%, respectively.
Conclusions The ICRP53 approach is not fully individualized (as required by the Italian law) given that it uses a fixed effective half-life of iodine dismissing phase. The algorithm provided by the AIMN guidelines overestimates the required activity in small pool syndrome patients because of the inability of the two parameters alone, namely effective half-life and maximum uptake, to characterize adequately the residence time. On the other hand, in the absence of OLINDA/EXM software, the EANM algorithm seems to predict quite well the required activity in patients with fast iodine metabolism.

Retrospective dose evaluation in 40 consecutive patients with diffuse autonomous goiter treated with radioidine

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Background Treating hyperthyroidism with radioiodine is a non expensive and easy-to-perform strategy in use worldwide. The dose delivered depends on several factors, such as thyroid uptake, activity administered, biological half-life of radioiodine, and thyroid mass. There are two well established approaches for estimating radioiodine activity to be administered: calculated and fixed activity. The calculated dose method is based on a dosimetric approach and involves uptake calculation and estimation both of effective (eff.) radioiodine biological half-life and of thyroid mass; with the fixed activity method no calculation is involved and a fixed activity of radioiodine, usually the largest

permitted for outpatients according to local laws, is administered.
Aim We set out to retrospectively evaluate the dose delivered to the thyroid in 40 consecutive patients with hyperthyroidism and diffuse autonomous goiter referred for radiotherapy and treated with the fixed activity method. To evaluate the response, we considered TSH levels over a one-year follow-up.
Methods All patients (13 M, age 52±18 years) underwent radioiodine therapy after a thyroid uptake test with 2.5 MBq of ^{131}INa. This was followed by thyroid uptake assessment at 6-24-48h, thyroid scan, and thyroid mass estimation by semi-automatic mass calculation using 20-30-40% scatter subtraction (SS). Twenty patients had also a diagnostic ^{99m}Tc-pertechnetate scan. At the time of treatment all patients had subclinical hyperthyroidism or euthyroidism, and were not receiving or had discontinued anti-thyroid therapy. The dose delivered to the thyroid was calculated using the formula D(dose)= [A(activity administered)/5.829)] x [Umax(uptake max) x 1/2(eff. half-life)/m(thyroid mass)].
Results Results were as follows: mean administered activity = 533.6 (SD ± 65.8)MBq; mean mass = 71.4 g (SD ± 29.7) with 20%SS, 46.6 g (SD ± 21.7) with 30%SS, 32.3 g (SD ± 15.9) with 40%SS; mean Umax = 52.2 % (SD ± 15.7); eff. half-life = 163.8 hrs (SD ± 51.8); dose delivered = 136.6 Gy (SD ± 88.4) with 20%SS, 231.4 Gy (SD ± 192.7) with 30%SS, and 352.8 Gy (SD ± 382.0) with 40%SS. A significant inverse correlation was observed between mass and dose delivered ($r = -0.63$ $p<0.05$), but not between effective half-life and Umax and dose delivered. Umax uptake was always observed after 24h. Mean mass evaluated with ^{99m}Tc-pertechnetate scan was 42g (SD ± 19.2); this value was significantly different compared to mass calculated on radioiodine scan evaluated with 20% SS and 40% SS ($p<0.05$), but not when compared to thyroid mass obtained with a cut-off of 30%SS (p: n.s.). In 10 patients the delivered dose was estimated ex post with a 30%SS and was found to be higher than 250 Gy, these patients were all hypothyroid at follow-up; conversely, of the 30 patients receiving less than 250 Gy, 12 (40%), who received a mean dose of 120 Gy, were still hyperthyroid at one year.
Discussion In this series of patients, thyroid mass seems to be the most critical variable for estimating the dose delivered to the thyroid. In our setting, the use of 30% background subtraction in a radioiodine scan, when compared with ^{99m}Tc-perrtecnetate scan and follow-up, seemed to be suitable for thyroid mass estimation. Moreover, since maximum thyroid uptake was never reached before 24 h, a two-point uptake, with the first point evaluated later than 24 h, seems to be appropriate for clinical purposes.
Conclusions Fixed radioiodine activity delivers a very wide and unpredictable range of doses to hyperfunctioning thyroid: we evaluated an easy and non expensive method of estimating the activity of radioiodine to be administered in order to obtain significant clinical results and also to adhere to optimization and good clinical practice principles.

Results of a prospective, randomized study of a novel method for calculating the personalized ^{131}I-iodide activity based on individual reduction of thyroid mass in Graves' disease

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Aim There is no consensus regarding the most appropriate dosimetric approach for treating Graves' disease with ^{131}I-iodine. This study shows the efficacy of a personalized approach based on the desired therapy-induced volume (mass) reduction, used in order to define the optimal activity of ^{131}I-iodine to be administered.
Methods A model for calculating the "optimal" final thyroid mass has been developed and published in recent years. It is based on sequential measurements of changes in thyroid volume, uptake and kinetics obtained in 40 patients with Graves' disease following ^{131}I-iodide therapy. Based on this model, the optimal thyroid final mass (m_{fin}) can be estimated as follows: $m_{fin}=0.24*m_0/U_0$ where m_0 and U_0 are baseline mass and maximum thyroid uptake, respectively. Starting from the MIRD equation and linear quadratic model in radiobiology, a final equation was developed to calculate the therapeutic activity based on the desired final mass of the gland. A total of 160 Graves' disease patients treated in our department were randomly divided into 5 groups based on the level of absorbed thyroid dose (ATD) from ^{131}I, equal respectively to 100 Gy (Group A, n=29), 200 Gy (Group B, n=25), 300 Gy (Group C, n=13), and 400 Gy (Group D, n=29); Group V included 64 patients who received a ^{131}I activity calculated on the basis of the "optimal" desired final thyroid mass.
Results At one-year follow-up, 14/29 patients in Group A (48%), 16/25 patients in Group B (64%), 28/29 patients in Group D (97%), and 60/64 patients in Group V (94%) were cured. A significantly higher proportion of patients were cured in Groups D and V than in Groups A and B ($p<0.01$), while there was no statistical difference between the cure rate in Group D versus Group V. The average ATD was 407±23 Gy in Group D, significantly higher than in Group V (277±75 Gy, $p<0.01$), as was the administered ^{131}I activity (524±201 MBq versus 386±173 MBq, $p<0.01$). Administered activities in Groups A and B were 223±201 MBq and 266±129 MBq, respectively, with average ATDs of 106±12 Gy and 204±9 Gy. Outcomes regarding cure rate of patients in Group C (average ATD 300±17 Gy) are still under evaluation. If the percentage of cured patients were similar to Group V, the administered activity would be higher than Group V (452 ±190 MBq versus 386±173 MBq).
Conclusions These results confirmed that our novel method based on thyroid mass reduction allows to optimize the ^{131}I-iodide therapy for Graves' disease on an individual basis obtaining a high therapeutic efficacy and avoiding administration of an unjustified higher activity of ^{131}I-iodine.

Results of a follow-up analysis for hyperthyroidism treatments with a customized dosimetric approach

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Aim Radioiodine therapy is currently the treatment of choice in most hyperthyroidism cases. The critical issue is that of the activities administered, which should be adequate for obtaining disease remission but as low as possible for radioprotection reasons. Leaving aside the administration of standard activities, dose optimization requires the identification of critical parameters, namely the maximum radioiodine uptake (U_{max}), the effective half-life of the radiotracer ($T_{1/2\text{-}eff}$) and the thyroid mass. A follow-up study was conducted at Sant'Anna Hospital in Como, assessing the effectiveness of a personalized radioiodine outpatient treatment for hyperthyroidism.
Materials and methods The clinical response of 135 patients undergoing ^{131}I-sodium iodide treatment was evaluated in a 6-year follow-up study. The sample comprised 78.5% females and 21.5% males, with mean age of 58.8 y. Patients were affected by Graves' disease (49.6%), single nodular goiter (35.6%) or multinodular goiter (14.8%). The study of functional thyroid mass, U_{max} and $T_{1/2\text{-}eff}$ was accomplished during the pre-treatment phase. Tomographic ^{99m}Tc-pertecnetate SPECT images were analyzed by a reconstruction process based on a 3D specific software, in order to determine the functional thyroid vol-

ume. U_{max} and $T_{1/2\text{-}eff}$ were identified studying the bi-exponential curve that fitted each patient's ^{131}I sodium-iodide uptake. Activity measurements were performed at 2, 24, 96 hours after the administration, with an additional measurement at 6 hours in Graves' disease patients. The treatment consisted of a single intravenous administration of ^{131}I. The post treatment follow-up was carried out through periodic hormone checks. The statistical analysis pertained to the healing dependence on thyroid mass, administered activities, doses, U_{max}, $T_{1/2\text{-}eff}$ and type of pathology, also considering the age and gender of patients.
Results A single treatment resulted in 85.1% remission in Graves' disease (75.4% in hypothyroidism and 24.6% in stable euthyroidism); no remission was obtained in 14.9%. All the patients undergoing a second treatment achieved total remission, all evolving into hypothyroidism with an average 65.2% mass reduction. In patients affected by uninodular or multinodular goiter, remission was achieved in 100% with a single treatment, evolving into euthyroidism (85.3%) or hypothyroidism (14.7%). The median recovery time was 4 months (IQR = 3÷6) for both nodular and Graves' pathologies. High variability was found for thyroid masses (5÷107.9 g), U_{max} (9.2÷82.2%) and $T_{1/2\text{-}eff}$ (37.9÷191.2 h). In the Graves' disease patients without remission after a single treatment, average thyroid mass was 50.2±25.4 g while for cured patients it was 33.0±13.1 g, whereas $T_{1/2\text{-}eff}$ and U_{max} were comparable. By consequence, even when administering slightly higher activities (A_{mean} = 557.3±116.4 MBq versus 497.7±146.5 MBq, $\Delta\%$ = 11.3%), prescribed doses were lower (D_{mean} = 192.2±52.7 Gy versus 224.9±102.1 Gy, $\Delta\%$ = -15.7%).
Conclusions The low frequency of re-treatments in Graves' disease and the total remission in nodular goiter patients indicate that customized radioiodine hyperthyroidism treatment, based on accurate dosimetry studies, is a very effective approach. Administered activities, not exceeding the 600 MBq limit for outpatient treatments imposed by Italian law, often entailed insufficient doses for larger thyroid masses in Graves' disease patients, resulting in the need for a second treatment. On the whole, personalization of activities using this customized dosimetry protocol allows more effective dose optimization with respect to the standardized activity approach, especially in view of the large inter-subject variability.

Red marrow dosimetry in radioiodine treatment of metastatic differentiated thyroid carcinoma: pre-treatment versus on-therapy preliminary results

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Background and aim Administered activity in metastatic differentiated thyroid carcinoma is often limited by hematological toxicity related to the dose delivered to red marrow. The Italian multicenter AIFM (Associazione Italiana di Fisica Medica) protocol was applied for extensive routine red marrow dose evaluations: operating procedures were analyzed and effectiveness of pre-treatment dosimetry was evaluated through comparison with on-therapy dosimetry results. Starting from this comparison, uncertainties in the methods are determined in order to allow safe escalation of individualized administered activity.
Methods Since January 2011 red marrow dosimetry has been performed routinely in patients affected by metastatic differentiated thyroid carcinoma. By September 2011, 26 patients had undergone 24 pre-treatment blood and red marrow dosimetry assessments and 33 on-therapy dose evaluations, according to the EAMN and AIFM methods. Generally, pre-treatment dosimetry was performed one week before radioiodine therapy by administering patients an oral tracer activity of ^{131}I (range 15.3-32.9 MBq). Starting from 2 h after administration, once a day, 4-5 blood samples were acquired and AP-PA whole-body measurements were performed using a Na^{131}I counter placed at a distance of 4 m from the patient's body. To perform on-therapy dosimetry, detectors placed on patients' beds provided whole-body AP counts (every 2 h, from 8.00 a.m. to 10.00 p.m). Blood samples were acquired once a day at 2 h after therapeutic activity administration (range 3745-7480 MBq). Residence times were obtained from bi- or monoexponential data fit (r^2>0.98). Data were collected in a dedicated database. Dose per unit activity to red marrow and to blood were calculated; percentage variation between preliminary and on-therapy values were evaluated (mean, standard deviation, range) as well as intra-therapy variability, among patients who underwent multiple treatments.
Results The mean (±1 st.dev.) absolute percentage difference between pre-treatment and on-treatment dosimetry results was 17.7±11.9% (range 0.2%-40.2%) with the EANM method and 16.9±10.5% (range 0.3%-35.5%) with the AIFM method; there was no significant difference between the two methods (t-test on the means, p>0.7). When pre-treatment dosimetry was compared to on-therapy dosimetry performed at a later date (more than 6 months), absolute percentage variation could rise to more than 30%. Data fit may influence the predictability, therefore it is important to apply the same model when analyzing pre-treatment and on-therapy data.
Conclusions We performed a comparative analysis between pre-treatment and on-therapy dosimetry. When performing pre-treatment red marrow dose estimations using the EANM or AIFM methods, it is necessary to take into account an overall uncertainty of 20%. It is also important to perform pre-treatment dosimetry before each treatment to take into account clinical variations. Further studies should be performed in order to confirm the present results on a larger dataset of patients.

RADIONUCLIDE THERAPY AND DOSIMETRY 2

Radioembolization with Yttrium-90 glass microspheres in patients with HCC: a prospective phase II study

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Aim Hepatocellular carcinoma (HCC), the third most common cause of cancer-related mortality, benefits from a curative surgical approach in a restricted number of patients. Radioembolization, a new concept in radiation therapy, has shown promising outcomes in primary and secondary liver malignancies. Radioembolization with Yttrium-90 (^{90}Y-RE) microspheres may represent an important tool in patients with intermediate-advanced hepatocarcinoma. The aim of this prospective phase II study was to assess the efficacy of Yttrium-90 microsphere radioembolization on time to progression (TTP). Secondary endpoints were tumor response, safety and overall survival (OS).
Materials and methods Fifty-two consecutive patients with intermediate (17) or advanced (35) unresectable HCC were enrolled. All patients were ECOG 0-1 and Child-Pugh stage A-B7. Pre-treatment

evaluation included: CT scan, α-fetoprotein (AFP) levels, liver function tests, ^{99m}Tc-macroaggregated albumin scan and angiography. Standard lobar treatments were performed to deliver a mean absorbed dose of 120 Gy to the target lobe. CT scan and biochemical markers were performed at 1 month and every 3 months to assess tumor response, according to RECIST, WHO and EASL criteria. Retrospective dosimetric evaluation was performed to correlate absorbed dose in target lesions with tumor response. Liver decompensation occurring within 6 months was considered treatment-related.

Results Fifty-eight treatments were performed in the 52 patients enrolled. The median injected activity was 2.6 GBq and the median dose to the liver lobe was 101 Gy. Median follow-up was 36 months. Median TTP was 11 months with no significant difference between portal vein thrombosis (PVT) vs noPVT (7 vs 13 mo). Median OS was 15 months (95%CI: 12-18) with a non-significant trend in favor of non-PVT vs PVT patients. The 2-yr progression rate was 62%. Objective response was 40.4%. Disease control rate (DCR: 78.8%) significantly affected 3-year survival (responders vs non-responders: 18.4% vs 9.1%). Tumor response significantly correlated with mean absorbed dose in target lesions and a tumor control probability of 50% was obtained at 500 Gy. The multivariate analysis showed that tumor response was the only variable affecting TTP ($p<0.001$) and the second, after Child-Pugh stage, affecting survival. Mortality at 30-90 days was 0%-3.8%. Liver decompensation occurred in 36.5% of patients, with no differences between PVT vs non-PVT patients, but with marked difference according to basal Child-Pugh. The risk of liver decompensation was correlated to parenchyma dose and, for the same dose, was higher for more advanced chirrotic stages.

Conclusions Radioembolization with Yttrium-90 microspheres is an effective and safe treatment in patients with intermediate-advanced HCC, particularly in cases of PVT. New dosimetric treatment planning may improve treatment efficacy. This study was partially supported by a grant from the Min. of Health (5 per mille) and Italian Association of Cancer (AIRC).

Correlation between liver toxicity after SIRT and voxel-based dosimetry on ^{90}Y-PET imaging

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Aim The purpose of this study was to evaluate by voxel dosimetry (VD) whether the radiation burden delivered to the whole liver after selective internal radiation therapy (SIRT) is correlated with the onset of early organ dysfunction (ascites, jaundice, encephalopathy).

Methods One hundred and thirty-seven patients with unresectable liver metastases were treated with SIRT between 2010 and 2012 in our section. In all cases a dedicated protocol was used to obtain ^{90}Y-PET images after SIRT. Among all these subjects, five patients with early liver dysfunction after administration of ^{90}Y-microspheres were included in this study and retrospectively evaluated by VD. Liver failure was observed at 3-5 weeks post treatment and death occurred 3-4 months post SIRT. The mean administered doses ranged from 1.3 GBq to 1.85 GBq, calculated with a BSA method. Two patients were submitted to a single SIRT session, while in 3 patients internal radiation therapy was repeated at 6 weeks after the previous session. VD was calculated only on the healthy liver. For each patient the average absorbed dose and the biological effective dose (BED) to liver were assessed. Furthermore, to compare the doses delivered during the SIRT procedure with external beam radiation therapy (EBRT), the absorbed doses to the liver were converted to an equivalent dose (EQ_2) delivered at 2 Gy/fraction ($\alpha/\beta=2.5$)

Results Qualitative evaluation of ^{90}Y-PET images showed distribution of microspheres in the healthy liver in all patients with no significant focal accumulation of microspheres on tumor sites. The two patients who underwent a single SIRT session received an average absorbed dose of 35.4 Gy (EQ_2=30.1 Gy, BED=54.2 Gy) and 38.5 Gy (EQ_2=33.4 Gy, BED=60.8 Gy). The three patients who underwent two-cycle treatments received a cumulative average dose ranging from 36.9 to 68.12 Gy (EQ_2 ranging from 27.0 to 58.3 Gy, BED ranging from 48.5 to 104.9 Gy). Interestingly, all patients presented areas on healthy liver receiving doses higher than 50 Gy, corresponding to BED values > 100 Gy.

Conclusions VD with ^{90}Y-PET can be a valuable procedure for predicting the onset of severe organ toxicity. The average absorbed dose to the whole liver can reach a critical level when ^{90}Y-microspheres do not properly accumulate within the lesions. A BED constraint of 64 Gy for the non-tumoral liver is generally considered during SIRT treatments, corresponding to EQ_2=35 Gy in EBRT. In our study, BED and EQ_2 values beyond these constraints were observed and a good correlation with liver toxicity was observed.

Treatment with tandem ^{90}Y-DOTA-TATE and ^{177}Lu-DOTA-TATE in patients with advanced neuroendocrine tumors refractory to conventional therapies

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Aim Neuroendocrine tumors (NETs) overexpress somatostatin receptors and efficacy of peptide receptor radionuclide therapy (PRRT) with somatostatin analogs labeled with β-emitting radioisotopes has been reported. A combination of different radionuclides with different energies, such as ^{90}Y and ^{177}Lu, could be advantageous, allowing the irradiation of both small and larger lesions, which are often found in these patients. ^{90}Y emits high-energy β-particles which travel longer distances and is therefore useful to irradiate large masses. On the other hand, ^{177}Lu β-particles have a short range of penetration allowing them to keep all the energy inside the targeted lesions, especially if small. The optimal radionuclides and treatment schedule with ^{90}Y-DOTA-TATE and ^{177}Lu-DOTA-TATE in the management of somatostatin receptor-positive tumors have yet to be defined, thus we designed a phase II clinical study with a combination of these two radiopharmaceuticals. The aim of the study was to evaluate the feasibility, efficacy and toxicity of a new tandem treatment with alternating cycles of ^{177}Lu- and ^{90}Y-DOTA-TATE in patients with disseminated NETs expressing somatostatin receptors and refractory to conventional therapy.

Materials and methods Patients with disseminated NETs were included in the study and treated with a maximum of alternating 6 cycles of ^{177}Lu-DOTA-TATE (5.55 GBq) and ^{90}Y-DOTA-TATE (2.6 GBq). Dosimetric evaluation was performed following the first administration of ^{177}Lu-DOTA-TATE. Hematological and renal toxicities were graded according to the NCI toxicity criteria. Response to treatment

was evaluated using the RECIST criteria. Quality of life was assessed before and after therapy completion.
Results Seventy-one consecutive patients (42 males, 29 females) with metastatic NETs and refractory to conventional therapies (52 gastro-entero-pancreatic NETs, 19 other primary sites) were included in the study. Reversible haematological toxicity grade 3-4 was rarely observed. No renal or hepatic toxicities were observed. The majority of patients with pre-treatment carcinoid syndrome benefitted from the therapy. The cumulative kidney BED value was below the toxicity limit in the majority of patients. At median follow-up of 29.9 months (IQ range 23.4-33 months), 41 patients were evaluated. Overall response (OR) was 58%. Treatment evaluation at six months showed: SD= 42%, PR= 39%, CR=5% and PD=14%. Global overall survival and progression-free survival at 24 months were 78.1% and 52.2% respectively.
Conclusions Our preliminary results show that combined PRRT associating two radioisotopes with different energies represents an innovative, safe and effective therapeutic approach in patients with metastatic NETs. The advantage of tandem therapy is that it results in longer survival without increasing hematological and renal toxicities. This study was partially supported by a grant from the Min. of Health (5 per mille) and Italian Association of Cancer (AIRC).

Safety and antitumor efficacy of ^{153}Sm-EDTMP and Docetaxel administered sequentially to patients with metastatic castration-resistant prostate cancer

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Background Prostate cancer is the most common malignancy and the second cause of cancer death in males in the Western world. About 10% to 20% of patients with newly diagnosed prostate cancer have metastatic disease. Metastases are responsible for most of the morbidity associated with metastatic castrate-resistant prostate cancer (mCRPC). Androgen withdrawal therapy is initially an effective form of treatment, but after a variable time prostate cancer progresses to a hormone-refractory state. When the tumor becomes castration-resistant, chemotherapy can prolong overall survival. Docetaxel-based therapy is currently the standard first-line chemotherapy in patients with mCRPC. Bone-seeking radiopharmaceuticals have been approved for palliation of painful skeletal metastases, but their clinical use is limited by concerns over toxicity levels, also from the perspective of combined treatment with chemotherapy agents. We investigated whether docetaxel administered to mCRCPC patients after treatment with ^{153}Sm-EDTMP would show increased toxicity and/or reduced antitumor efficacy.
Patients and methods Thirty mCRPC patients with skeletal metastases were enrolled. Patients received standard therapy with docetaxel (75 mg/m^2 i.v. every 21 days for at least 6 cycles) on average 6 weeks after ^{153}Sm-EDTMP (37 MBq/kg). In addition to monitoring for toxicity, antitumor efficacy was assessed by changes in serum PSA levels.
Results Over 80% of the patients (25/30) showed favorable biochemical responses. Median time to progression was 9.1 months (mean 9.8, 95% CI 7.8-9.9), while median overall survival was 19.9 months (mean 24.5, 95% CI 16.9-22.8); five patients were still alive over 5 years after enrollment. Hematological toxicities observed after both treatments were as expected when administering the docetaxel alone. Hematological toxicity of variable degrees constituted the main side effect both of treatment with ^{153}Sm-EDTMP and of subsequent therapy with docetaxel, while no non-hematological toxicity events were reported. None of the patients required support therapy for the above hematological toxicities.
Conclusions Prior administration of ^{153}Sm-EDTMP does not imply additional toxicity for subsequent treatment with docetaxel and seems to improve the antitumor efficacy of the latter. This work justifies - further investigations into the possible synergistic effects of combined strategies with the two agents.

^{131}I-MIBG radionuclide treatments: whole-body dose versus activity per kg in adults and children

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Aim To assess the most accurate method for delivering ^{131}I-MIBG therapy, by optimizing administered activity. Hematological toxicity following ^{131}I-MIBG treatment was compared with dosimetry estimations, expressed as whole-body (WB) dose and Gy/GBq, and with administered activity per kg.
Methods From September 2003 to June 2012 a total of 22 patients, respectively 9 children and 13 adults treated with MIBG therapy at our institution, underwent dosimetry measurements. Of these, 12 patients were affected by neuroblastoma, 8 patients by pheochromocytoma or paraganglioma, and 2 patients by medullary thyroid carcinoma. Dose estimations, performed according to the MIRD method, using planar scintigrams and/or probes at predetermined intervals (from 1 hr to 168 hrs), were correlated with activity per kg, tumor extension and uptake, bone marrow (BM) toxicity and recovery and finally with the effects of the treatment. Hematological toxicity was investigated by weekly blood samples until hematological recovery. Six autologous stem cell transplantations were performed 2 weeks after MIBG therapy in 4 patients (3 children, 1 adult).
Results Fifty dosimetry studies were performed in total, 26 in neuroblastoma cases (16 in children, 10 in adults) and 24 in the other tumours (all adults). Administered activity ranged from 7.4 to 16.65 GBq, corresponding in children to 5-21 mCi/kg (median 10 mCi/kg) and in adults to 3-7 mCi/kg (median 5 mCi/kg). Grade II/III BM toxicity was observed in all children and in 6/13 adult patients, while in all the remaining 7 adult patients transient grade I BM toxicity was present after the first treatment. In any case the grade II/III toxicity was reversible, without severe adverse effects, even though in 4 cases it persisted for 3 to 6 months. In children, WB dose ranged from 1 Gy to 3.6 Gy (median 1.7 Gy), in adults from 0.55 to 1.87 Gy (median 0.96 Gy). The dose was near or equal to 2 Gy in 5/16 child studies (range 1.8-2.0) and in 3/34 adult studies (1.8-1.9 Gy). One child received a dose of 3.6 Gy (0.4 Gy/GBq), corresponding to an activity of 18 mCi/kg. In 16 patients, studied two to four times, both WB and tumour dose lowered after the II course and the grade and the length of toxicity worsened after any further treatment. In children, the WB absorbed dose did not correlate with activity per kg, while in adults the Spearman coefficient was 0.84 ($p<0.0001$). This may be explained by the larger relative tumor/WB mass uptake ratio in children compared with adults.
Conclusions In children, BM toxicity was systematic as a consequence of higher WB absorbed doses, but .in most cases it was expected, as related to the high pro/kg activity administered and consequently MIBG treatment was planned in conjunction with the autologous stem cell infusion. In adults, toxicity was not predictable, even when WB absorbed dose was less than 2 Gy; this was because individual BM radio resistance or reserve predominates over the irradiation effects. Given that after each treatment WB and tumor dose lowered but toxicity worsened, every effort should be made to optimize the administered activity at the first therapy, by means of a systematic dosimetry study with ^{131}I or ^{124}I-MIBG.

MISCELLANEOUS

Evaluation of renal function in elderly patients: performance of creatinine-based formulae versus the [^{99m}Tc]DTPA method

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Background and aim Measurement of glomerular filtration rate (GFR) and urinary protein secretion is recognized worldwide as the most accurate way of assessing kidney function. The prevalence of impaired renal function increases with advancing age. The gold standard methods to test renal function, such as inulin clearance, [^{51}Cr]EDTA, and [^{99m}Tc]DTPA, are rarely applied in routine clinical practice, and there exist various formulae developed as possible clinical alternatives: the Cockcroft-Gault (CG) formulae, the Isotope Dilutions Mass Spectrometry-Modification of Diet in Renal Disease (IMDS-MDRD) formula, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. In this study we used different methods to evaluate kidney function in elderly subjects over and under the age of 70 years, trying to establish which formula produces the best measurement of renal function in this population.
Materials and methods Patients needing GFR measurement and renal scintigraphy, for various clinical problems, were randomly selected from two age groups [<70 years (n=37) and ≥70 years (n=39)]. [^{99m}Tc]DTPA (trade name: TechneScan®DTPA) was prepared and controlled in accordance with the European Pharmacopoeia.We injected each patient with approximately 180 MBq of [^{99m}Tc]DTPA. Two plasma samples were collected at 60 and 180 minutes after injection applying Charles D. Russell's two-sample method, using a vein other than the one used for injection. We compared [^{99m}Tc]DTPA GFR values with the following formulae used in clinical practice: CG real weight, CG normalized weight, IMDS-MDRD and CKD-EPI.
Results In patients aged <70 years, no statistically significant difference was found between GFR evaluated with [^{99m}Tc]DTPA and GFR values obtained using the other methods: CG real weight (p=0.23), CG normalized weight (p=0.31), IMDS-MDRD (p=0.54), and CKD-EPI (p=0.38). In patients age ≥70 years, no statistically significant difference was found between GFR evaluated with [^{99m}Tc]DTPA and GFR evaluated using the CG real weight formula (p=0.97). Conversely, statistically significant differences were found between GFR evaluated with [^{99m}Tc]DTPA and GFR values obtained using the CG normalized weight (p=0.002), IMDS-MDRD (p=0.024), and CKD-EPI (p=0.028) formulae.
Discussion and conclusions In patients <70 years of age there were no statistically significant differences, in GFR values, between [^{99m}Tc]-DTPA and all the clinical formulae. By contrast, in patients older than 70 years, the use of the two "classical" formulae (IMDS-MDRD and CKD-EPI) overestimated GFR in stage III CKD (GFR 30-60 ml/min) when compared to the gold standard [^{99m}Tc]DTPA method. Thus, in subjects aged >70 years only the CG real weight formula provided results comparable with [^{99m}Tc]DTPA-assessed GFR. However, since the correlation (R^2=0.68) is weak, this latter finding needs to be confirmed in larger patient series. In conclusion, in elderly patients, GFR measured using "classical" serum creatinine-based formulae may be overestimated compared to [^{99m}Tc]DTPA GFR.

^{99m}Tc-mebrofenin scintigraphy in the evaluation of liver function in patients with Wilson's disease

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Wilson's disease (WD) is a rare autosomal recessive disorder that is characterized by decreased biliary copper excretion and defective incorporation of copper into ceruloplasmin, leading to copper accumulation mainly in the liver, brain and kidneys. Clinical manifestations related to copper accumulation in the liver include hepatic disease ranging from mild hepatitis to acute liver failure or cirrhosis. The purpose of this study was to establish whether ^{99m}Tc-mebrofenin dynamic hepatobiliary scintigraphy (DHBS) can be used to assess liver function in WD.
Material and methods We studied 37 consecutive WD patients treated with zinc and/or penicillamine (18 males and 19 females; mean age 39±4 years) with clinical evidence of hepatic disease. All patients underwent standard biochemical liver function tests, including ALT, AST,GGT, AP, TOT BIL, ALB, serum copper and ceruloplasmin and 24-h urinary copper excretion, and DHBS with ^{99m}Tc mebrofenin. Liver biopsies were performed in all WD patients. Liver tissue was examined for routine liver histology (grading and staging of fibrosis) and hepatic copper content. DHBS acquisitions (30 sec/frame for 60 min) were obtained after 110 MBq ^{99m}Tc mebrofenin i. v. injection. Time-activity curves were recorded from regions of interest placed over hepatic parenchyma (H) and main intra-hepatic biliary ducts (B). The times required to reach 50% of the hepatic activity peak (50% HTmax), maximal hepatic activity (HTmax), and the time to reach 50% of decrease of HTmax ($HT_{1/2}$) were calculated. Furthermore, the times at biliary maximum peak counts (BTmax) and to half of peak activity ($BT_{1/2}$) were calculated. Quantitative scintigraphic results were compared to biochemical parameters and liver histopathology.
Results All patients showed low levels of serum ceruloplasmin and copper, respectively (3.05±0.2mg/dl and 57±18µg/dl) and high 24h urinary copper excretion (201±42µg/24h). According to Metavir fibrosis staging, 16 patients (43%) were classified as F1, 7 as F2 (19%), 8 as F3 (22%) and remaining 6 as F4 (16%). The analysis of DHBS quantitative data showed, in almost patients, slow hepatic uptake (>HTmax) and hepatobiliary excretion (>$HT_{1/2}$). A positive correlation was observed between histological findings and 50% HTmax (p= 0.004), HTmax (p=0,001), $HT_{1/2}$ (p=0.006) and BTmax (p=0.02) values. Furthermore, on multivariate analysis, a statistically significant correlation was found between 50% HTmax, HTmax, $HT_{1/2}$, BTmax and high degree of fibrosis (F4) vs other degree of fibrosis. With the exception of bilirubin (p<0.01), no correlation was found between biochemical liver function tests and DHBS parameters.
Conclusions This study showed the clinical utility of the DHBS as non-invasive diagnostic modality for evaluating the degree of liver fibrosis, making it possible to reduce the number of liver biopsies in the long-term follow-up of WD patients.

Quantitative bone uptake of ^{99m}Tc-HMDP, serum bone turnover markers, and whole-body and lumbar spine DEXA in adult kidney transplant patients

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Background Quantitative studies of bone metabolism using ^{99m}Tc-diphosphonates have a potential role in the investigation of patients with metabolic bone disease and their response to therapy. The aim of this study was to validate global and regional (trabecular and cortical) skeletal uptake of ^{99m}Tc-diphosphonates according to Brenner's method in adult kidney transplant patients.
Methods Fifty-two consecutive patients were evaluated at least 6 months after kidney transplant by whole-body and lumbar spine DEXA, parathyroid hormone (PTH), 25[OH]-vitamin D, C-terminal telopeptide (cTx), (bone) alkaline phosphatase, creatinine serum samples and serial (t = 3', 1, 2, 3, 4 and 24 hours) bone scanning after i.v. injection of 740 MBq of ^{99m}Tc-HMDP. Bone uptake (BU) was quantified according to Brenner's modified method. Regional (trabecular and cortical) metabolism indexes were also derived from DEXA bone mineral content (BMC) and ROI on lumbar vertebrae and proximal femur. No patient was under treatment with diphosphonates. Mean glomerular filtration rate (GFR) was 57 ml/min ± 17 (range 30-94).
Results Mean BU of ^{99m}Tc-HMDP at 3 hours after injection was 43% ± 8.1 (range 25-58). Normal BU derived from the literature is lower (~ 25-30%). An inverse correlation between GFR and BU ($r = -0.33$; $p < 0.05$) was found. There emerged a positive correlation between trabecular metabolic index and whole-body DEXA BMC ($r = 0.33$; $p < 0.05$) and an inverse correlation between regional proximal femur ^{99m}Tc-HMDP uptake and femoral DEXA BMC ($r = -0.8$; $p < 0.01$). In patients with preserved renal function (GFR ≥ 70 ml/min [n = 9]), regional trabecular metabolism indexes (femur and lumbar ROIs) showed an inverse correlation with PTH, a cortical bone resorption hormone ($r = -0.64$; $p < 0.05$); in patients with GFR < 70 ml/min the strong correlation found between BU, GFR and cTx hampers significant correlations of regional metabolic indexes. Other correlations between BU, PTH, 25[OH]-vitamin D, calcium, whole-body DEXA derived BMC, lumbar and femoral DEXA and (bone) alkaline phosphatase were found.
Conclusions Global and regional skeletal uptake of ^{99m}Tc-diphosphonates according to Brenner's method allows non-invasive insights into regional cortical and trabecular bone metabolism in adult kidney transplant patients with preserved renal function. ^{99m}Tc-HMDP uptake and derived indexes of trabecular bone metabolism have a potential role in the diagnosis, management and treatment response evaluation of metabolic bone disease.

Intraoperative hand-held γ-camera for sentinel node detection in patients with breast cancer. Feasibility evaluation and preliminary experience in 16 patients

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Aim To assess the feasibility and potential usefulness of an intraoperative portable high-resolution γ-camera for sentinel lymph node (sLN) localization in patients with breast cancer.
Methods Sixteen T1-T2 female breast cancer patients (mean age 62 years, range 46-80) were evaluated with preoperative lymphoscintigraphy. All patients presented with an ultrasound-guided cutaneous mark on the overlying skin perpendicular to the tumor site where an intradermal injection of 60-70 MBq of ^{99m}Tc-nanocolloids in saline volumes of 0.1-0.2 ml was performed. Lymphoscintigraphy consisted of a standard anterior and oblique anterior planar acquisition of the thorax starting 10-30 min after the injection. In some cases extra projections or late images (2-4 hours post-injection) were also obtained to better identify the SLNs and to assess their exact number. Surgery took place the following day (18-20 hours after tracer injection) in a different hospital, which does not have a nuclear medicine unit. For intraoperative SLN localization a traditional γ-probe was used by the surgeon who removed all radioactive nodes he identified. Afterwards, the nuclear medicine physician, present in the operating room, evaluated the surgical area with the portable hand-held γ-camera, searching for other "missed" radioactive nodes. Every removed node was checked "ex vivo" both by the γ-probe and the γ-camera to confirm that they were radioactive. The findings of the three methods (lymphoschintigraphy, γ-probe and imaging with a γ-camera) were compared and the opinion of the surgeon about the contribute during surgery was obtained.
Results The portable γ-camera for intraoperative imaging showed very high spatial resolution (2.4 mm) in the 4.4x4.4 cm^2 field of view, with a good sensitivity of 180 cps/MBq at a plexiglass depth of 1 cm. In the whole series of 16 patients the lymphoscintigraphy identified 27 radioactive spots, whereas the portable γ-camera identified 28. A total of 28 radioactive lymph nodes were removed at surgery and sent to pathology. In 8 patients, lymphoscintigraphy, γ-probe and portable imaging γ-camera depicted the same number of lymph nodes (12 nodes; 5 of which were metastatic and detected in 5 different patients). In three patients the γ-probe and the portable imaging γ-camera depicted fewer nodes than the lymphoscintigraphy (5 instead of 9, one of which was metastatic). In five patients the portable imaging γ-camera depicted one node more than lymphoscintigraphy (11 instead of 6, in total 5 nodes more), one of which was metastatic (the only metastatic on that patient).
Discussion The portable γ-camera proved to be very effective in detecting the exact number of radioactive lymph nodes in real time during the operation. Another important role of the γ-camera was to confirm the dissection of all radioactive nodes and document their removal through intraoperatively saved images. Moreover, it was useful in the visualization of nodes characterized by a slow drainage and with a relatively low radiotracer uptake that were therefore not well depicted by lymphoscintigraphy. The portable γ-camera may also be useful when lymphoscintigraphy is not available.
Conclusions Use of the portable hand-held high-resolution γ-camera is a feasible and non-invasive and non-time-consuming procedure for intraoperative sentinel node localization, offering extra confidence to the surgeon.

Measuring glucose consumption by dynamic FDG imaging to estimate cancer metabolism and evaluate treatment response to Sorafenib in a mouse model of intracranial gliobastoma: an *in vitro* and *in vivo* study

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Background Glioblastoma (GBM) is a highly aggressive CNS tumor that relapses at high rates after surgery and radio/chemotherapy. This

characteristic is related to infiltration of the normal parenchyma and to resistance to cytotoxic and radiation therapy. The development of therapies for GBM has been limited by difficulties in assessing treatment effectiveness over time using non-invasive imaging. Our aim was to estimate the potential of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in the evaluation of GBM metabolism and tumor response to Sorafenib, a multikinase inhibitor.

Materials and methods Cancer cells were obtained from tumor specimens surgically harvested from GBM patients who had never received therapy. GBM cells were expanded *in vitro* in stem cell medium and analyzed for the expression of neural stem cell markers, multilineage differentiation and tumorigenicity. *In vitro* glucose consumption was evaluated by incubating 10^6 cells with 1 ml of saline containing 148 KBq of ^{18}F-FDG. Tracer exposure was maintained for one hour at 37°C before measuring labeling yield with a gamma-counter. Evaluations were performed under control conditions and under Sorafenib at a concentration of 15 μM. Two different times of drug exposure were used just before labeling: 1 or 3 hours, respectively. The *in vivo* study was completed in 21 NOD/SCID mice divided into three groups: eleven GBM animals received intracranial administration of 500000 (GBM Untreated), five GBM mice underwent micro PET analysis during-Sorafenib treatment (GBM Active Treatment) (60 mg/kg by gavage) and five mice were used as controls. A bolus of 3-6 MBq of FDG was injected through a tail vein, during a list mode acquisition lasting one hour using a dedicated micro PET system (Albira, Carestream Inc.). After framing rate optimization, tumor glucose consumption was measured using the Patlak graphical approach and normalizing the slope of regression line for serum glucose level.

Results *In vitro* exposure of GBM cells to Sorafenib significantly decreased FDG uptake with respect to the control condition ($p<0.01$ vs control) independently of exposure time (1 hours and 3 hours). A similar effect was observed *in vivo*. Brain glucose consumption was markedly higher in untreated GBM animals with respect to control ones (1.35±0.16 vs 0.75±0.21 microMol X g^{-1} X min^{-1}, respectively, $p<0.05$). Sorafenib treatment decreased glucose uptake to values similar to those of sham mice (0.76±0.16 microMol X g^{-1} X min^{-1}, $p<0.05$ vs untreated, ns vs controls).

Conclusions The coherence between *in vitro* and *in vivo* experiments indicates that dynamic micro-PET analysis of glucose consumption can be used in mouse models of intracranial GBM to evaluate the therapeutic potential of innovative treatments for this cancer type. These preliminary data provide a rationale for possible development of studies focusing on Sorafenib as potential treatment of malignant glioblastoma.