activity by PET. Proof that these probes can measure the inhibition of proliferation in the absence of tumour shrinkage has been provided for trichostatin-A in HT29 tumour bearing mice. The relationship between inhibition of proliferation and specific effects of the drug including histone H4 hyperacetylation has been studied. Clinical validation of 2-[^{11}C]thymidine has also been performed. The retention of 2-[^{11}C]thymidine was shown to correlate with MIB 1 index in gastrointestinal cancers of patients.

Angiogenesis, the development of new blood vessels from preexisting host vessels is mediated by growth factors, the most important of which is vascular endothelial growth factor (VEGF). A novel PET imaging agent for VEGF, [^{124}I]anti-VG76e, has been developed. [^{124}I]anti-VG76e is immunoreactive and has been shown to differentially label human xenografts that express different levels of VEGF. Imaging studies demonstrated maximal localisation of [^{124}I]anti-VG76e at 24 h post injection. In addition to angiogenesis, evaluation of the magnitude, spatial distribution and time course of gene expression can enhance the scientific impact of gene therapy trials. We have employed a marker gene-PET marker substrate paradigm to monitor gene expression *in vivo*. Promoters of interest have been used to drive marker genes (HSVI-thymidine kinase or sodium iodide symporter). Gene expression is determined indirectly by imaging the retention of PET probes, which are substrates for the protein product of the marker gene.

Dihydropyrimidine dehydrogenase (DPD) is the proximal and rate limiting enzyme in the catabolism of 5-fluorouracil. Large variations in enzyme expression occur and have been shown to influence the pharmacodynamics of 5-fluorouracil. Eniluracil is a mechanism-based inactivator of DPD. Proof of mechanism of action of eniluracil in patients was provided by studying the *in vivo* pharmacokinetics of 5-[^{18}F]fluorouracil (5-[^{18}F]FU) by PET. The rapid conversion of 5-[^{18}F]FU by normal liver (the organ with the highest DPD activity) to [^{18}F]fluoro-β-alanine, as well as the hepatobiliary excretion of [^{18}F]fluoro-β-alanine bile conjugates were inhibited by eniluracil. In the tumours of these patients, the reduction in catabolism led to a significant increase in tumour 5-[^{18}F]FU + anabolite levels.

892 POSTER

The role of FDG whole body positron emission tomography in metastatic carcinoma of unknown primary site

M. Osborne, A. Makris, P.J. Hoskin, J. Lowe, J. Emmott, W.L. Wong.
Mount Vernon Hospital, Northwood, UK

Aim: 5-6% of new cancer cases present as cancer of unknown primary site. They represent a heterogeneous group of tumours, often requiring extensive investigation. The subgroup of patients presenting with extracervical metastases tend to have a worse prognosis and whole body imaging with a non-invasive modality in this group is appealing. The aim of this study was to evaluate the role of FDG PET in establishing a primary tumour in this group and assess its influence on their management.

Patients and Methods: 25 patients (13 male, 12 female) mean age 58 years (range 35-86), with histologically (17) or cytologically (8) confirmed metastatic carcinoma were imaged with whole body PET following conventional work up which failed to reveal the primary origin. Sites of presenting metastases were liver (8 patients), bone (5), nodes (4), ascites (2), and mediastinum, scalp, brain, pelvis, chest wall, abdominal wall (1 each). Investigations prior to PET scanning incuded CT scanning in all cases and mammography, endoscopy, MRI, serum tumour markers and immunohistochemistry according to clinical suspicion of primary tumour site. Whole body scan was performed at one hour post injection of 350MBq of FDG.

Results: In all cases the known sites of metastases were confirmed on PET and in 68% of patients other metastatic sites were also identified. 14/25 (56%) PET scans suggested a possible primary site - lung (4), pancreas (3), breast (1), renal (1), oesophagus (1), caecum (1), colon (2), stomach (1). Of these, 1 primary was subsequently confirmed. In one case a primary not visible on the original PET scan was subsequently identified and confirmed on biopsy in the pancreas. 9/25 (36%) PET scans had some influence on management- 8/25 (32%) supported the planned treatment, but only 1/25 (4%) actually altered planned treatment.

Conclusion: In this group of patients with metastatic carcinoma of unknown primary origin PET identified the known metastases in all cases. Although a possible primary was identified in 56%, this could not be confirmed in the majority of cases. The influence on patient management was limited.

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The value of positron emission tomography (PET) for individual therapeutic management in localised cancer of unknown primary (CUP)

D. Rades[1], I. Wildfang[1], G. Kuehnel[2], A.R. Boerner[2], W. Knapp[2], J.H. Karstens[1]. [1]*Dept. of Radiation Oncology and Dept. of Nuclear Medicine [2], Hannover Medical University, Hannover, Germany*

Background: 2-4% of cancer patients present with CUP syndrome. Median survival for localised disease is 20, for disseminated disease 7 months. For localised disease individual therapeutic strategies become more important, as an option for curative treatment is more likely. After conservative diagnostic procedures including MRI and endoscopy the primary is detected in less than 25%. The diagnostic value of PET and its influence on therapeutic strategies were evaluated prospectively.

Patients and methods: From 05/98 to 10/00 a total of 42 patients, 30 female and 12 male, with localised CUP were investigated. Median age was 60 (42-77) years. Presenting site was lymph node metastasis in 34 patients (cervical 25, axillary 5, inguinal 2, mediastinal 1, paraaortal 1), and visceral metastasis in 8 patients (bone 4, liver 2, pleura 1, CNS 1). Distribution of histologies was squamous cell carcinoma 24, adeno carcinoma 10, anaplastic carcinoma 7, and small cell carcinoma 1. After a median of 7 (3-11) diagnostic procedures without detection of primary, but evidence of localised disease, PET was performed with Fluorine-18-fluorodeoxyglucose.

Results: In 26/42 patients (62%) a primary was suggested by PET and later on confirmed (histologically) in 18 patients (43%): carcinoma of the lung 5, tonsil 2, parotis 2, oral cavity 1, hypopharynx 1, larynx 1, breast 1, liver 1, ovary 1, vagina 1, urethra 1, and anus 1. In 5 of these 18 patients beyond localised disease, additional dissemination, not detected by previous diagnostic measures, was diagnosed by PET. Overall, dissemination was detected only by PET in 16/42 patients (38%). In 29/42 patients (69%) the PET result had major influence on selection of definitive palliative or curative treatment (mostly as radiochemotherapy or radiotherapy alone), in 13 patients by detection of the primary, in 11 patients by detection of dissemination, and in 5 patients by detection of both primary and dissemination. After a median follow up of 11 (3-33) months, 1-year-OAS was 77% (17/22): 100% (14/14) for localised and 38% (3/8) for disseminated disease ($p = 0.012$). 1-year-PFS was 60% (15/25) for the whole series: 93% (13/14) for localised and 18% (2/11) for disseminated disease ($p = 0.009$).

Conclusion: In patients with CUP the PET result has major impact on detection of the primary as well as of disseminated disease. Furthermore, it has also relevant consequences on the individual therapeutic management.

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Phase II of cisplatin (CDDP), etoposide (VP16) and gemcitabine (G) in cancer of unknown primary (CUP)

C. Balaña, M. Margelí, J. Manzano, T. Moran, A. Font, A. Abad, R. Rosell.
Hospital Universitari 'Germans Trias i Pujol', Medical Oncology, Badalona/Barcelona, Spain

Purpose: New agents are beeing incorporated to the treatment of CUP. Addition of G to VP16 & CDDP could cover pancreatic and lung cancer which are the commonest origin of this disease. A combination of the 3 drugs was performed in order to study tolerability, and activity measured as the response rate and overall survival.

Methods: All multiple-organ CUP patients (p), with normal renal and liver function were treated with CDDP 70mg/m2 d1, plus VP16: 70mg/m2d 1 & 2 and G 700mg/m2 d 1 & 8, every 21 d. Assessment of toxicity on each cycle (c).Evaluation of response after 3c. G was administered on d 8 if WBC*1500x109 and platelets 100.00x109. G-CSF was administered in subsequent cycles in case of a neutropenic fever.

Results: 18p (15M/3F), Median age 64.5 (33-74y), 14 adenoc (ac), 3 carcinoma (c), 1 squamous cell c, 11p(61.4)*3 invaded sites, K I*70: 90%, 2p brain metastasis. 76 c, 72c evaluable for toxicity, 16p evaluable for response. Response rate was: CR 2 (12.5%) PR 5 (31.3%) SD 4 (25%) PD 5 (31.3%). (ORR: 43.8%). Principal toxicity was mielosuppression. Nadir was on day 15: leucocytes GIII-IV: 18%c, granulocytes 47%c, platelets 11%c. 6(37%)p had a neutropenic fever and needed G-CSF to continue treatment.

Conclusions:CDDP+VP16+Gemcitabine is an active combination in UPC, principal toxicity is mielosuppresion. More data will be shown, as the study is ongoing.