Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

Clinical Cancer Research

Imaging, Diagnosis, Prognosis

^{18}F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors

Tina Binderup[1,2], Ulrich Knigge[2,3], Annika Loft[1], Birgitte Federspiel[4], and Andreas Kjaer[1,2]

Abstract

Purpose: ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is currently not used on a routine basis for imaging of neuroendocrine (NE) tumors. The aim of this study was to investigate the prognostic value of FDG-PET in patients with NE tumors.

Experimental Design: Ninety-eight prospectively enrolled patients with NE tumors underwent FDG-PET imaging. FDG uptake was quantified by maximal standardized uptake value (SUVmax). The prognostic value of FDG uptake, proliferation index, chromogranin A, and liver metastases were assessed.

Results: During the 1-year follow-up, 14 patients died. The diagnostic sensitivity of FDG-PET was 58% (n = 57) and a positive FDG-PET result was associated with a significantly higher risk of death with a hazard ratio (HR) of 10.3 [95% confidence interval (CI), 1.3-78.9]. Thirteen of the 57 (23%) FDG-PET–positive patients died compared with 1 of 41 (2%) FDG-PET–negative patients. By univariate analysis, a SUVmax of >9 and a high Ki67 index were significant predictors of overall survival with a HR of 8.8 (95% CI, 2.7-28.7) and a HR of 2.6 (95% CI, 1.3-5.1), respectively. In a multivariate analysis including a SUVmax of >3, Ki67, and chromogranin A, SUVmax of >3 was the only predictor of progression-free survival (HR, 8.4; $P < 0.001$).

Conclusions: This study shows a strong prognostic value of FDG-PET for NE tumors, which exceeds the prognostic value of traditional markers such as Ki67, chromogranin A, and liver metastases. FDG-PET may obtain an important role for NE tumors. *Clin Cancer Res; 16(3); 978–85. ©2010 AACR.*

Surgical resection is the only treatment that is able to cure patients with neuroendocrine (NE) tumors. However, for patients with unresectable disseminated disease, the treatment strategy and clinical outcome varies considerably. Based on the suspected aggressiveness of the disease, patients are given different treatment regimens. The medical approach is based on either symptomatic treatment with somatostatin analogues or α-IFN, which is preferred for the least aggressive tumors or a more aggressive approach for the rapidly proliferating tumors, generally using systemic chemotherapy. For patients with disseminated disease and a positive somatostatin receptor scintigraphy (SRS), peptide receptor radionuclide therapy based on somatostatin analogues labeled with a β-emitting isotope for local irradiation of the tumor is also an option for treatment. Furthermore, new therapy options under clinical evaluation, which are targeting angiogenesis, tyrosine kinases, or serine threonine kinases, seem promising for the treatment of NE tumors (1–3).

For the early selection of patients who will benefit from more aggressive treatment, validated prognostic factors are crucial. Currently, patients are selected based on the presence of metastases, elevated plasma chromogranin A (CgA) levels, localization of the primary tumor, and the high proliferation rate of the tumor as determined by immunohistochemical staining for Ki67. For staging of disease, determination of the proliferation rate is mandatory. However, in surgically unresectable patients, biopsy of the tumor is required for the determination of the Ki67 index, which is not always a trivial procedure, and the tissue obtained is not necessarily representative of the whole tumor in terms of aggressiveness.

Noninvasive functional imaging with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) seems promising as an alternative to tissue sampling for the determination of the aggressiveness of tumors (4) and has prognostic value in several cancer forms. Accordingly, it is now used in patients with pulmonary cancer (5–7), Hodgkin's lymphoma (8, 9), head and neck cancer (10), and colorectal cancer (11–13) for diagnosis; monitoring of treatment; and as a prognostic tool. However, FDG-PET is currently not used for NE tumor imaging on a routine basis because these tumors are generally slow growing and, accordingly, have low glycolytic activity compared with many other malignancies that therefore may lead to a low sensitivity for FDG-PET. Furthermore, the current gold

Authors' Affiliations: [1]Department of Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet, [2]Cluster for Molecular Imaging, Faculty of Health Science, University of Copenhagen, [3]Department of Surgical Gastroenterology, Rigshospitalet, and [4]Department of Pathology, Rigshospitalet, Copenhagen, Denmark

Corresponding Author: Andreas Kjaer, Rigshospitalet, Department of Clinical Physiology, Nuclear Medicine and PET, 4011, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark. Phone: 45-35-32-75-04; Fax: 45-35-32-75-46; E-mail: tinab@mfi.ku.dk.

doi: 10.1158/1078-0432.CCR-09-1759

Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

Translational Relevance

Neuroendocrine (NE) tumors are a heterogeneous group of neoplasms with great variability in clinical outcome. This requires accurate diagnostic techniques for precise staging and choice of therapy. Today, the grading of NE tumors is mainly based on the immunohistochemical determination of the proliferation marker, Ki67. However, pathologic examination on biopsy or resected specimens may not be representative of the whole tumor burden, and whole-body noninvasive alternatives are warranted. In this study, we show a high prognostic value of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) for predicting the survival of patients with NE tumors. The prognostic value of FDG-PET was compared with the value of traditional markers for NE tumors, such as proliferation index, computed tomography–verified liver metastases, and plasma chromogranin A levels. FDG-PET and Ki67 index were the only independent predictors of overall survival. This observation suggests FDG-PET as a valuable noninvasive supplement or alternative to grading based on the proliferation index as well as for detection of disease progression.

standard for functional imaging, In-111-diethylenetriaminepentaacetic acid-octreotide, has a high sensitivity and specificity for visualization of NE tumors. Studies on small groups of patients with NE tumors suggest that FDG-PET may be of value for the imaging of the more aggressive tumors with high Ki67 indices (14, 15). The anticipated variable uptake of FDG in NE tumors may reflect differences in aggressiveness and, thus, FDG-PET may hold prognostic information for these tumors. To our knowledge, the prognostic potential of FDG-PET for NE tumors has never been evaluated.

The aim of the present study was, therefore, to investigate the prognostic value of FDG-PET in NE tumors. To do so, we performed a prospective study of FDG-PET and overall survival (OS) in a cohort of 98 consecutive patients with NE tumors.

Patients and Methods

Patients. From May 2007 to June 2008, 98 consecutive patients with NE tumors (47 men and 51 women; mean age, 60 y; range, 21-81 y) were prospectively enrolled in the study at the Department of Surgical Gastroenterology C, Copenhagen University Hospital, Rigshospitalet, which is a tertiary referral hospital and center for treatment of patients with NE tumors. The follow-up continued until February 2009. Inclusion criteria were (*a*) histologically verified NE tumors of gastroenteropancreatic origin or lung origin (typical and atypical bronchial carcinoids) and (*b*) the presence of primary, residual, or recurrent disease (primary tumor, metastases, or both) upon enrollment in the study.

The study population consisted of 45 intestinal carcinoid tumors, 30 functioning and nonfunctioning pancreaticoduodenal NE tumors, 8 typical or atypical broncho-pulmonary carcinoid tumors, 6 colonic NE tumors, and 2 poorly differentiated NE tumors with other primary localization (bile duct and stomach). In addition, seven patients had liver metastases with an unknown origin of the primary NE tumor. Patient characteristics are shown in Table 1.

Written informed consent was obtained from all participants and the study had been approved by the regional scientific ethical committee.

All aspects of patient care and treatment were carried out at the discretion of the treating clinicians and according to routine procedures of the department. Treating clinicians were blinded to the FDG-PET results and the FDG-PET results were not used for treatment decisions. The treatment given during follow-up is summarized in Table 1. Patients were treated in accordance with European guidelines for NE tumors (16). Patients with hormonal symptoms and diarrhea received treatment with somatostatin analogues, and depending on proliferation index, tumor origin, and treatment tolerance, patients were treated either with α-IFN (least aggressive) or systemic chemotherapy (more aggressive). Patients with disseminated disease, normal kidney function, and a positive SRS were treated with peptide receptor radionuclide therapy. Patients with liver metastases were in selected cases treated with radiofrequency ablation or liver embolization.

As part of the routine follow-up, half-yearly or yearly, patients were followed by plasma CgA measurements and diagnostic computed tomography (CT) of the abdomen. Relevant CgA measurements were available for 97 patients and relevant CT images were available for 94 patients. These CT images were used for the analysis of the prognostic value of CT-verified liver metastases. In addition, the routine CT images were used for the evaluation of progression-free survival (PFS) according to the Response Evaluation Criteria in Solid Tumors criteria (17). Tumor burden was evaluated by an expert in radiology as part of the clinical routine and the CT image closest to and before the FDG-PET scan was used as baseline. Time to progression was calculated as the time from the FDG-PET scan until tumor progression.

Immunohistochemical evaluation of Ki67. Ki67 index was determined for patients whenever possible as part of the clinical routine either on resected tumors or from biopsies. Formalin-fixed, paraffin-embedded tissue samples were cut at 4-μm thick sections and were mounted on coated slides. Antigens were retrieved with DAKO Target Retrieval Solution, High pH for 20 min at 97°C (Code K8002) using the DAKO pretreatment link (DAKO,). After blocking the endogenous peroxidase activity with DAKO EnVision Flex+ (DAKO K8002) for 5 min, tissue sections were incubated with Monoclonal Mouse Anti-human Ki67 Antigen, DAKO Code M7240, at a dilution of 1:200 for 20 min at room temperature.

Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

Table 1. Patient characteristics

Characteristics	*n* (%)
Gender	
Male	47 (48%)
Female	51 (52%)
Age, mean (range)	
At diagnosis	55.9 (21-81 y)
At FDG-PET	60.0 (21-81 y)
Follow-up (mo), mean (range)	
From diagnosis	61.9 (1-334 mo)
From FDG-PET	11.5 (0.13-21.1 mo)
Type of tumor	
Intestinal carcinoid	45 (46%)
Colonic NE tumor	6 (6%)
Pancreatica-duedenal NE tumor	30 (31%)
Typical and atypical bronchial carcinoid	8 (8%)
Other & unknown primary with metastases	9 (9%)
Metastatic disease	
Yes	85 (87%)
No	11 (11%)
Unsettled	2 (2%)
Liver metastases	
Yes	62 (63%)
No	32 (33%)
Unsettled	4 (4%)
Ki67 proliferation index	
≤2%	47 (48%)
>2% ≤15%	27 (28%)
>15%	14 (14%)
Missing	10 (10%)
Ki67 proliferation index determined on	
Resected tumor	45 (51%)
Biopsy	43 (49%)
Elevated CgA (above 130 pmol/L)	
Yes	73 (74%)
No	24 (25%)
Missing	1 (1%)
Markedly elevated CgA (above 460 pmol/L)	
Yes	50 (51%)
No	47 (48%)
Missing	1 (1%)
Treatment during follow-up	
Somatostatin analog	27 (28%)
α-IFN	29 (30%)
Chemotherapy, 5-fluorouracil/Zanosar	25 (26%)
Chemotherapy, other	7 (7%)
Radiofrequency ablation	5 (5%)
Liver embolization	4 (4%)
PRRT	28 (29%)
Surgery	12 (12%)

The reaction was visualized by using DAKO EnVision Flex+ mouselink for 15 min followed by DAKO EnVision Flex+/horseradish peroxidase for 20 min and finally DAKO EnVision Flex+ diaminobenzidine for 10 min. The sections were counterstained with hematoxylin for 1 min. A section of the human tonsil was used as a positive control. Reading of slides was done by counting positive tumor nuclei per 100 tumor cells.

FDG-PET/CT. PET/CT images were acquired 1 h postinjection of 342-467 MBq F-18-FDG. Blood glucose was measured before the FDG injection, and for all patients, the level was ≤8 mmol/l.

The PET/CT scans were done either by a GE Discovery LS PET/CT scanner or a Siemens Biograph 16 PET/CT scanner. The scanners used in the study were calibrated on a regular basis to ensure similar standardized uptake value (SUV) values on both scanners. Emission scan time was 3 min per bed position. The CT scans were done as low-dose CT scans with 10 mA for minimization of the radiation burden. The CT data were used for attenuation correction of the PET data. The PET and low-dose CT images were reconstructed in all three planes and were fused and analyzed on the GE eNTEGRA PET workstation and Siemens Leonardo workstation, respectively. The low-dose CT images were used as anatomic guides for the localization of the pathologic foci.

All patients were instructed to fast for at least 6 h before the F-18-FDG injection. All images were analyzed by an expert in nuclear medicine who also quantified the tracer accumulation [expressed as maximum SUV (SUVmax) calculated as radioactive concentration in target tissue/(injected dose/body weight)] in the primary tumor and the metastasis (if any) with highest FDG uptake in the PET-positive scans. The SUVmax was not calculated in PET scans without pathologic foci and these patients were included in the survival analyses with the SUVmax value zero.

Statistics. The sample size was determined on basis of an ability to detect a hazard ratio (HR) of 3 or more with a significance level of 0.05, and a power of 0.8 with an assumed median time to death in the group with highest mortality of 30 mo. With 100 patients accrued over 12 mo, this would need a follow-up interval of 21 mo.

For the study of the prognostic value of FDG-PET, PFS, and OS were chosen as end points. PFS was defined as the time from FDG-PET acquisition to progression or disease-related death. Overall survival was defined as the time from FDG-PET acquisition to death by any cause. In one case, the patient committed suicide and was censored from the PFS analysis at the time of death but was maintained in the analysis of OS. There were no other deaths unrelated to the NE tumor diagnosis.

Survival probability and PFS was estimated by the method of Kaplan and Meier, and significance was tested by the log-rank test. The assumption of proportional hazard was tested by means of plotting partial residuals (Schoenfeld residuals) against time. The plots were inspected visually following line fitting using the locally weighted scatterplot

Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

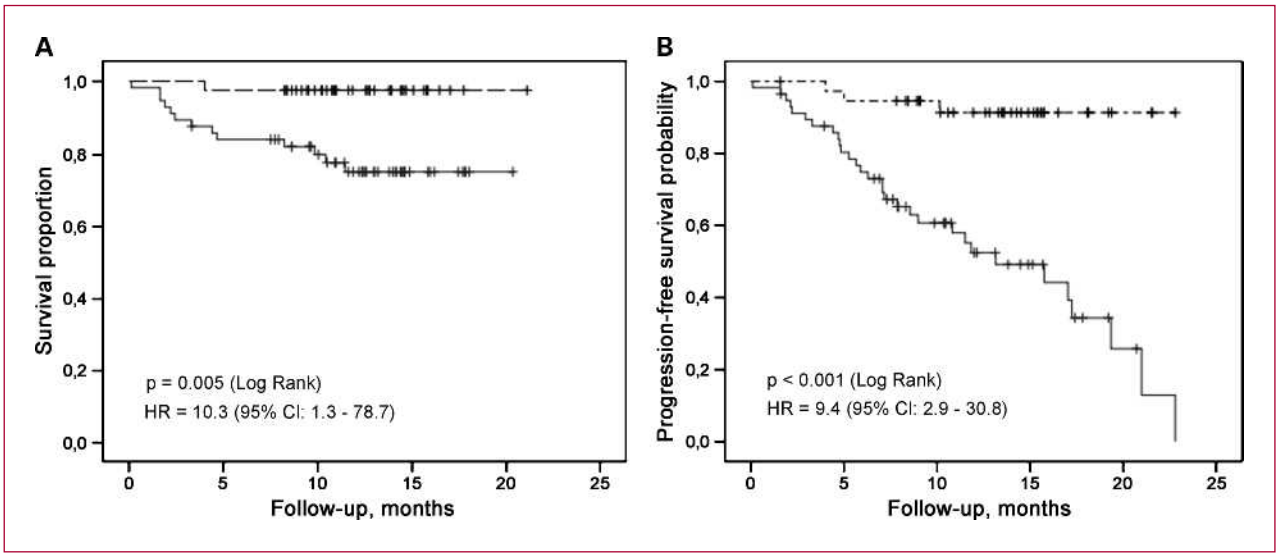

Fig. 1. A, survival distribution among patients in the FDG-PET–negative (black, dashed) or FDG-PET–positive (black, solid) groups. B, PFS distribution for the FDG-PET–positive (black, solid line) and the FDG-PET–negative (black, dashed line) groups.

smoothing (LOESS) iterative algorithm. The multivariate analyzes were carried out using the Cox proportional hazard regression analysis.

The Ki67 index was categorized according to the WHO 2000 criteria, in which NE tumors are divided into well-differentiated endocrine tumors (Ki67 < 2%), well-differentiated endocrine carcinomas (Ki67 between 2% and 15%), and poorly differentiated endocrine carcinomas (Ki67 > 15%; ref. 18). CgA levels were dichotomized by the median value to minimize the likelihood of inadvertent bias, which could be the result of data-determined cutoff values. For 2 × 2 tables, a χ^2 test was used. All data analyses were carried out using the SPSS version 16.0 (SPSS, Inc.). $P < 0.05$ was considered significant.

Results

A total of 98 consecutive patients with histologically verified NE tumors were enrolled in the study and all had FDG-PET imaging performed. The mean follow up time after the FDG-PET scan was 11.5 months (range, 4 days to 21.1 month). One patient, with a newly diagnosed pancreatic NE tumor (glucagonom), a Ki67 proliferation index of 100%, and progressive disease died 4 days after the FDG-PET scan due to his NE tumor. Fourteen patients had died at the end of the follow-up period. Of the 14 deaths in the survival analysis, 13 were FDG-PET positive and 1 was FDG-PET negative (small intestinal carcinoid; χ^2: $P = 0.007$). The mortality group consisted of three small intestinal carcinoids, five pancreatic NE tumors, one bronchial carcinoid, and four colonic NE tumors. During the follow-up period, 12 patients had surgery.

Of the 98 included patients, FDG-PET was positive in 58% ($n = 57$) and negative in 42% ($n = 41$) of the cases. The overall risk of death was significantly higher in the FDG-positive group than the FDG-negative group with a HR of 10.3 [95% confidence interval (CI), 1.3-78.7]. The Kaplan-Meier curve of FDG-PET is shown in Fig. 1A (log rank $P = 0.005$. For comparison, PFS for the FDG-PET–positive group and the FDG-PET–negative group is shown in Fig. 1B. Patients in the FDG-PET–positive group had a significantly lower PFS compared with the FDG-PET–negative group with a HR of 9.4 (95% CI, 2.9-30.8; log rank: $P < 0.001$). Quantification of the tracer accumulation calculated as SUVmax revealed a higher risk of death for patients with a SUVmax above 9 with a HR of 8.8 (95% CI, 2.7-28.7). The Kaplan-Meier curve is shown in Fig. 2A (log rank $P \leq 0.001$). The analysis of PFS revealed a lower PFS for patients with SUVmax above 3 with a HR of 8.9 (95% CI, 2.7-29.5; $P < 0.001$). The results of the other cutoff values of SUVmax for overall and PFS are listed in Table 2.

The Ki67 index was available in 88 patients (12 of 13 in the mortality group), of which 43 were derived from resected specimens and 45 from biopsy. The median (interquartile range) time interval from Ki67 index examination to the FDG-PET scanning was 7.7 (range, 1.1-47.9) months. Using the proliferation stratification values of 2% and 15% according to the WHO criteria (18), there was a significantly higher risk of death with increasing Ki67 index with a HR of 2.6 (95% CI, 1.3-5.1). A Kaplan-Meier curve with the OS based on Ki67 categorization according to the WHO criteria is shown in Fig. 3A (log rank $P < 0.001$). Using a cutoff value of 15% for the Ki67 index, there was a significantly higher risk of death for patients with a Ki67 index above 15% with a HR of 7.4 (95% CI, 2.5-22.1; log rank $P < 0.001$). Additionally, PFS decreased with higher Ki67 proliferation index with a HR of 2.7 (95% CI, 1.7-4.4; $P < 0.001$; Fig. 3B).

Analysis of the FDG-PET results according to the WHO classification revealed that 19 of 47 patients (40%) with

Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

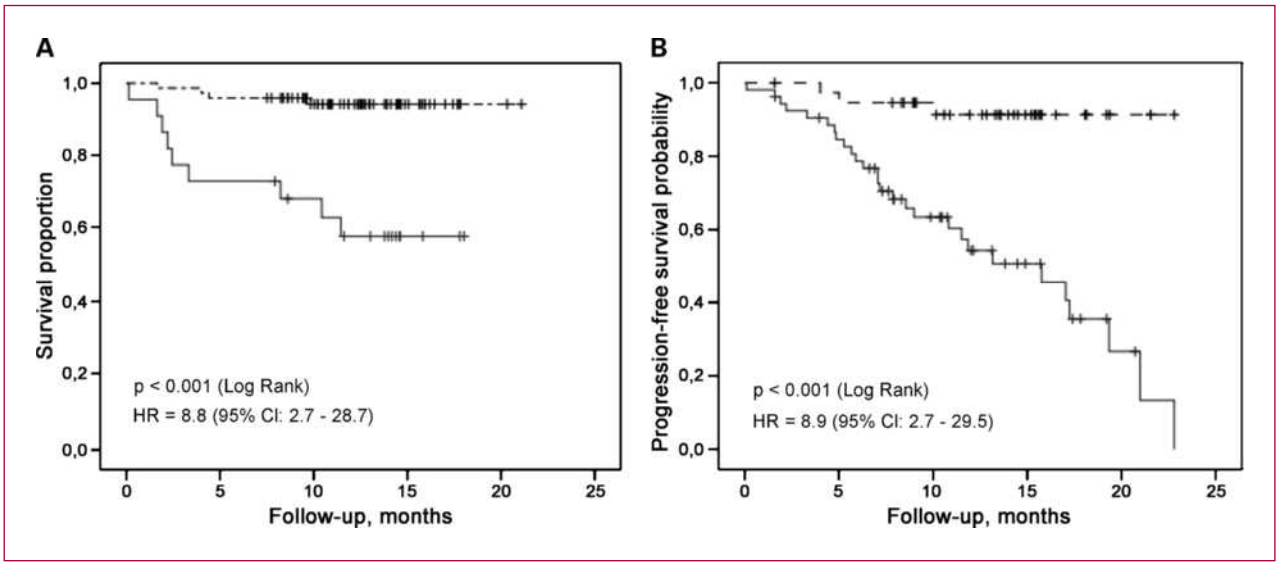

Fig. 2. A, survival distribution among patients with SUVmax below (black, dashed line) or above (black, solid line) 9. B, PFS distribution among patients with SUVmax below (black, dashed line) or above (black, solid line) 3.

a proliferation index below 2% were FDG positive, 19 of 27 patients (70%) with proliferation index between 2% and 15% were FDG positive, and 13 of 14 patients (93%) with proliferation index above 15% were FDG-PET positive.

In 94 patients, diagnostic CT imaging of the abdomen was available. Liver metastases were detected in 62 of 94 patients, but the survival analysis revealed no difference in the mortality rate for patients with and without CT-verified liver metastases (log rank $P = 0.255$; Fig. 4A). Additionally, when using the number of liver metastases (≥5 versus <5), no difference in survival was found in our material. The analysis of PFS supported the analysis of OS and did not reveal any significant difference in PFS between patients with or without CT-verified liver metastases (log rank $P = 0.406$; Fig. 4A).

Plasma CgA at the time of the FDG-PET scan was available for 97 patients. The median plasma CgA level was 460 pmol/L for all patients. In the univariate analysis, there was no significant difference in mortality for plasma CgA levels above or below 460 pmol/L (HR, 2.0; $P = 0.192$; 95% CI, 0.7-6.1). Other cutoff values of CgA up to 5,000 pmol/L were also tested, but there were no significant differences in mortality regardless of the cutoff value. In addition, there was no significant difference in PFS between patients with CgA levels above or below 460 pmol/L (HR, 1.6; $P = 0.154$; 95% CI, 0.8-3.3).

Due to the few events, multivariate analysis could not be applied for the OS. In a multivariate Cox proportional hazard regression analysis applied to PFS ($n = 84$; 28 events), with a median CgA level of 460 pmol/L, Ki67 index categorized according to the WHO criteria (<2%, between 2% and 15%, and >15%), and FDG-PET result entered in the model, FDG-PET result and Ki67 index remained statistically significant predictors of PFS with HRs of 1.8 and 6.0 (95% CI, 1.7-21.1 and 1.04-3.0; $P = 0.005$ and $P = 0.035$, respectively). When SUVmax with a cutoff value of 3 replaced FDG-PET result in the model, only SUVmax remained as a statistically significant predictor of PFS with a HR of 8.4 (95% CI, 2.5-27.9; $P = 0.001$.

Table 2. Univariate analysis of OS and progression free survival, SUVmax

Overall survival	HR	*P*	95% CI
SUVmax > 7	4.3	0.009	1.3-14.3
SUVmax > 8	6.1	0.001	1.8-20.2
SUVmax > 10	5.5	0.001	1.7-17.4
PFS			
SUVmax > 4	5.4	<0.001	2.1-14.0
SUVmax > 5	3.7	0.001	1.7-8.4
SUVmax > 6	2.8	0.005	1.3-5.9

Discussion

The variable aggressiveness and clinical outcome of NE tumors make the selection of an optimal treatment strategy challenging. Good and validated prognostic factors are needed to predict the aggressiveness of the tumor and thereby the optimal treatment for each patient. With the results of this prospective study we show that there is a strong prognostic value of FDG-PET for prediction of the OS of patients with NE tumors in which a HR

Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

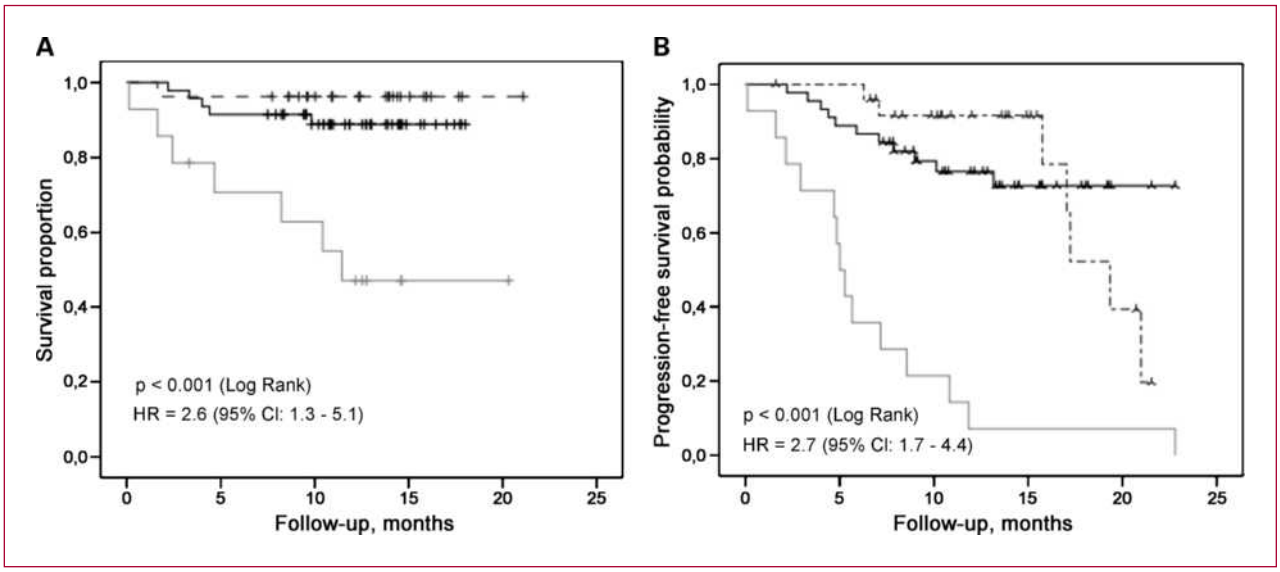

Fig. 3. A, survival distribution among patients with proliferation index below/at 2% (black, solid line), between 2% and 15% (black, dashed line), and above 15% (gray, solid line). B, PFS distribution among patients with proliferation index below/at 2% (black, solid line) between 2% and 15% (black, dashed line), or above 15% (gray, solid line).

of 10 for risk-of-death was found for patients with FDG-PET–positive foci compared with FDG-PET–negative patients.

In contrast to other and generally more aggressive cancer forms, in which FDG-PET is gaining widespread use for staging of disease, for treatment monitoring, and as a prognostic tool, the imaging modality of FDG-PET is at present not used clinically for NE tumors. The assumption has been that due to the low proliferation rate and low metabolic activity generally seen in these tumors, FDG-PET would have a low sensitivity and not provide additional information to conventional CT and SRS (15, 19–22). Studies on small groups of patients have confirmed this hypothesis, although FDG-PET tended to be positive for the low-differentiated NE tumors (14, 19). The low diagnostic sensitivity of FDG-PET for NE tumors was confirmed in the present study in which we found an overall sensitivity of 58%. In comparison, SRS is known to have a sensitivity of ~90% for NE tumor diagnostics (23–25).

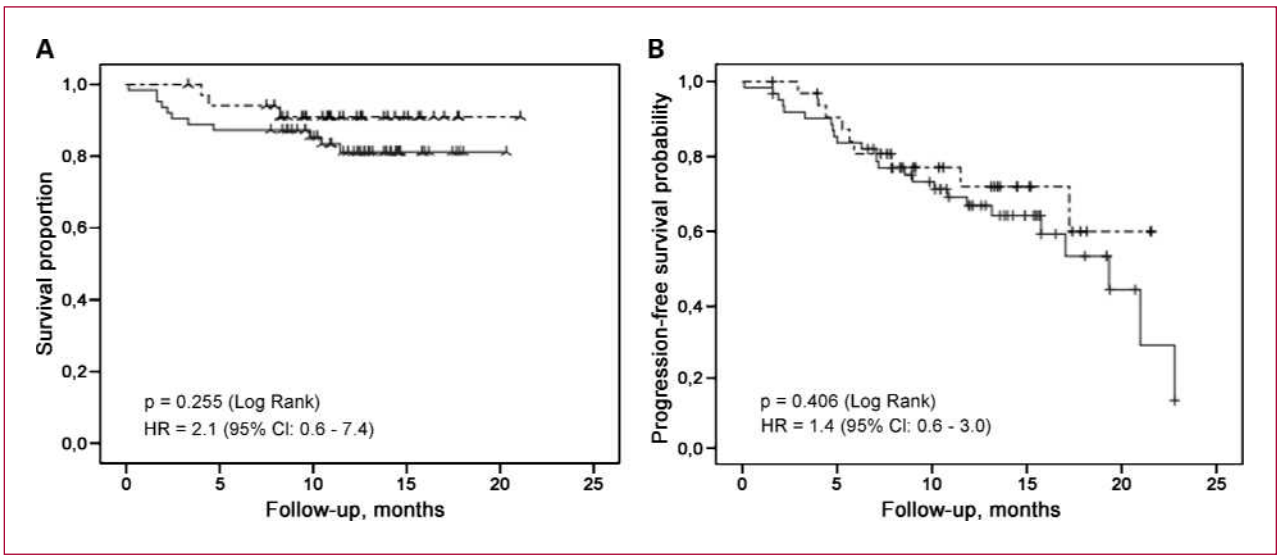

Fig. 4. A, survival distribution among patients without CT-verified liver metastases (black, dashed line) or with liver metastases (black, solid line). B, PFS distribution among patients without CT-verified liver metastases (black, dashed line) or with CT-verified liver metastases (black, solid line).

Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

Despite a high diagnostic sensitivity of SRS, the imaging modality gives limited information about the aggressiveness of the NE tumor, which can vary considerably. With this study, we have shown that although the diagnostic sensitivity of FDG-PET is low for NE tumors, the prognostic value is high. This makes the low diagnostic sensitivity less important because a negative FDG-PET result is predictive of low aggressiveness and a high survival rate (6, 7, 9). This study shows, both in univariate analysis and multivariate analysis, that FDG-PET, both in terms of positive/negative and quantified by SUVmax, was an independent prognostic factor for the prediction of survival for NE tumor patients, exceeding the prognostic value of traditionally used parameters such as Ki67, CgA level, and the presence of liver metastases. The analysis of PFS confirmed the survival data with a statistically significant difference in PFS between the FDG-positive and the FDG-negative group.

In this study, five of the tumors in the mortality group (38%) had a proliferation index below 2% and four of these had FDG-PET–positive foci. FDG-PET is considered to have a limited value in particular for slowly proliferating NE tumors with corresponding lower metabolic activity. In accordance with this, we found that 40% of patients with proliferation index below 2% were FDG positive compared with 70% of patients with proliferation index between 2% and 15%, and 93% of patients with proliferation index above 15%. However, this study shows that even for patients with a low Ki67 proliferation index, FDG-PET may be positive and indicate poor survival. Because the proliferative activity is currently determined through tissue collected by tumor resection or ultrasonographically guided needle biopsy, repeated measurements over time is not practically feasible and the proliferation index will only be determined on a randomly selected part of a tumor not necessarily representative of the patient's whole tumor burden. In contrast, FDG-PET is a noninvasive, whole-body imaging technique visualizing all aggressive tumors and metastases simultaneously. The discrepancy between a positive FDG-PET scan and a low proliferation index for four of the cases in the mortality group could be due to the dedifferentiation of the tumor from the time of Ki67 evaluation to the FDG-PET scan. However, in the four cases in the mortality group with positive FDG-PET scans and low proliferation index, the median time from Ki67 evaluation to FDG-PET examination was 4.9 months, which was shorter than the median time interval of 8.3 months for the rest of the patients.

Despite the high OS for patients with NE tumors, the cancer often metastasize to the liver over time, and the 5-year survival rate for patients with liver metastases has been reported to be between 50% to 85% depending on treatment, with the presence of liver metastases being associated with decreased 5- and 10-year survival rates (26–29). Whereas the diagnostic sensitivity of CgA is well validated (30), the prognostic value of CgA for prediction of survival in a cross-sectional measurement is less evident, despite some findings to the contrary (31–33). In this study, with a follow-up of ~1 year, we did not find a significantly higher mortality or lower PFS for the patients with CT-verified liver metastases or for patients with markedly elevated plasma CgA. The relatively short follow-up in this study may partly explain this, and in this respect, it seems that FDG-PET at a much earlier stage can better predict survival than the presence of liver metastases or elevated CgA levels. For a validation of these findings, longer follow-up is however needed because it is possible that it may not be applicable to all patients with NE tumors and the survival data may differ with a longer follow-up.

Patients with NE tumors remain a very heterogeneous group, both in terms of symptoms, clinical course, treatment strategy, and OS. The fact that FDG-PET overall predicts survival for NE tumors points to the high clinical effect this imaging modality could have in the future selection of appropriate treatment for each patient. Perhaps FDG-PET should be included in the follow-up and initial staging in this patient group to reveal high aggressiveness at an earlier stage and thereby be able to initiate a correspondingly more aggressive treatment approach for the most malignant NE tumors. FDG-PET may very well be the desired prognostic factor, which has been lacking for NE tumor staging. Because Ki67 index, as a marker of proliferation rate in the tumor, also predicted survival in the univariate analysis and due to the central role of Ki67 evaluation in the treatment planning of NE tumors, it is possible that the proliferation tracer F-18-fluoro-thymidine could be a useful tracer for staging of NE tumors and for treatment evaluation. Whether FLT-PET adds information or performs better than FDG-PET has yet to be determined in a comparative study in this patient population.

In conclusion, this study for the first time shows a strong prognostic value of FDG-PET for NE tumors, which exceeds the prognostic value of traditional markers such as Ki67, CgA, and liver metastases. Despite the convincing results, further studies are needed with longer follow-up for validation of these findings. If confirmatory, we suggest that FDG-PET may become an important routine-imaging modality for NE tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

Danish Cancer Society (A. Kjaer and T. Binderup), the Danish Medical Research Council, the Ministry of the Interior and Health, the National Advanced Technology Foundation, the John and Birthe Meyer Foundation, the A P Møller Foundation, the Lundbeck Foundation, the Novo Nordisk Foundation and the Svend Andersen Foundation. (A. Kjaer).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 7/8/09; revised 11/2/09; accepted 11/23/09; published OnlineFirst 1/26/10.

Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

References

1. Duran I, Kortmansky J, Singh D, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. Br J Cancer 2006;95:1148–54.
2. Kulke MH, Stuart K, Enzinger PC, et al. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol 2006;24:401–6.
3. Kulke MH, Lenz HJ, Meropol NJ, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol 2008;26:3403–10.
4. Vesselle H, Schmidt RA, Pugsley JM, et al. Lung cancer proliferation correlates with [F-18]fluorodeoxyglucose uptake by positron emission tomography. Clin Cancer Res 2000;6:3837–44.
5. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 2000;343:254–61.
6. Downey RJ, Akhurst T, Gonen M, et al. Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. J Clin Oncol 2004;22:3255–60.
7. de Geus-Oei LF, van der Heijden HF, Corstens FH, Oyen WJ. Predictive and prognostic value of FDG-PET in nonsmall-cell lung cancer: a systematic review. Cancer 2007;110:1654–64.
8. Hutchings M, Loft A, Hansen M, et al. FDG-PET after two cycles of chemotherapy predicts treatment failure and progression-free survival in Hodgkin lymphoma. Blood 2006;107:52–9.
9. Gallamini A, Hutchings M, Rigacci L, et al. Early interim 2-[18F]fluoro-2-deoxy-D-glucose positron emission tomography is prognostically superior to international prognostic score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol 2007;25:3746–52.
10. Torizuka T, Tanizaki Y, Kanno T, et al. Prognostic value of 18F-FDG PET in patients with head and neck squamous cell cancer. AJR Am J Roentgenol 2009;192:W156–60.
11. Park IJ, Kim HC, Yu CS, et al. Efficacy of PET/CT in the accurate evaluation of primary colorectal carcinoma. Eur J Surg Oncol 2006;32:941–7.
12. de Geus-Oei LF, Ruers TJ, Punt CJ, Leer JW, Corstens FH, Oyen WJ. FDG-PET in colorectal cancer. Cancer Imaging 2006;6:S71–81.
13. Wiering B, Krabbe PF, Jager GJ, Oyen WJ, Ruers TJ. The impact of fluor-18-deoxyglucose-positron emission tomography in the management of colorectal liver metastases. Cancer 2005;104:2658–70.
14. Pasquali C, Rubello D, Sperti C, et al. Neuroendocrine tumor imaging: can 18F-fluorodeoxyglucose positron emission tomography detect tumors with poor prognosis and aggressive behavior? World J Surg 1998;22:588–92.
15. Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer 2008;112:2447–55.
16. Plockinger U, Rindi G, Arnold R, et al. Guidelines for the diagnosis and treatment of neuroendocrine gastrointestinal tumours. A consensus statement on behalf of the European Neuroendocrine Tumour Society (ENETS). Neuroendocrinology 2004;80:394–424.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al, European Organization for Research and Treatment of CancerNational Cancer Institute of the United StatesNational Cancer Institute of Canada. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205–16.
18. Oberg K, Astrup L, Eriksson B, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine tumours (including bronchopulmonary and thymic neoplasms). Part I-general overview. Acta Oncol 2004;43:617–25.
19. Belhocine T, Foidart J, Rigo P, et al. Fluorodeoxyglucose positron emission tomography and somatostatin receptor scintigraphy for diagnosing and staging carcinoid tumours: correlations with the pathological indexes p53 and Ki-67. Nucl Med Commun 2002;23:727–34.
20. Sundin A, Eriksson B, Bergstrom M, Langstrom B, Oberg K, Orlefors H. PET in the diagnosis of neuroendocrine tumors. Ann N Y Acad Sci 2004;1014:246–57.
21. Adams S, Baum R, Rink T, Schumm-Drager PM, Usadel KH, Hor G. Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. Eur J Nucl Med 1998;25:79–83.
22. Adams S, Baum RP, Hertel A, Schumm-Drager PM, Usadel KH, Hor G. Metabolic (PET) and receptor (SPET) imaging of well- and less well-differentiated tumours: comparison with the expression of the Ki-67 antigen. Nucl Med Commun 1998;19:641–7.
23. Binderup T, Knigge U, Mogensen AM, Hansen CP, Kjaer A. Quantitative gene expression of somatostatin receptors and noradrenaline transporter underlying scintigraphic results in patients with neuroendocrine tumors. Neuroendocrinology 2008;87:223–32.
24. Kaltsas G, Korbonits M, Heintz E, et al. Comparison of somatostatin analog and meta-iodobenzylguanidine radionuclides in the diagnosis and localization of advanced neuroendocrine tumors. J Clin Endocrinol Metab 2001;86:895–902.
25. Kaltsas GA, Mukherjee JJ, Grossman AB. The value of radiolabelled MIBG and octreotide in the diagnosis and management of neuroendocrine tumours. Ann Oncol 2001;12 Suppl 2:S47–50.
26. Panzuto F, Nasoni S, Falconi M, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. Endocr Relat Cancer 2005;12:1083–92.
27. Frilling A, Li J, Malamutmann E, Schmid KW, Bockisch A, Broelsch CE. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg 2009;96:175–84.
28. Knox CD, Feurer ID, Wise PE, et al. Survival and functional quality of life after resection for hepatic carcinoid metastasis. J Gastrointest Surg 2004;8:653–9.
29. Shebani KO, Souba WW, Finkelstein DM, et al. Prognosis and survival in patients with gastrointestinal tract carcinoid tumors. Ann Surg 1999;229:815–21.
30. Bajetta E, Ferrari L, Martinetti A, et al. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer 1999;86:858–65.
31. Pape UF, Berndt U, Muller-Nordhorn J, et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer 2008;15:1083–97.
32. Nykjaer KM, Gronbaek H, Nielsen DT, Christiansen P, Astrup LB. Description of patients with midgut carcinoid tumours: clinical database from a Danish centre. In Vivo 2007;21:679–84.
33. Janson ET, Holmberg L, Stridsberg M, et al. Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. Ann Oncol 1997;8:685–90.

AACR American Association for Cancer Research

Clinical Cancer Research

^{18}F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors

Tina Binderup, Ulrich Knigge, Annika Loft, et al.

Clin Cancer Res 2010;16:978-985. Published OnlineFirst January 26, 2010.