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Neuroendocrine Neoplasms: Radiologic-Clinical Correlation

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Table of Contents

1. Abstrakt	5
2. Abstract	7
3. Introduction	9
4. Methods	11
5. Results	14
6. Discussion	16
7. References	19
8. Statutory Declaration	22
9. Declaration of selected publications	23
10. Selected Publications	
Publication 1	25
Publication 2	37
Publication 3	47
11. Curriculum Vitae	59
12. Publications	63
13. Acknowledgements	67

Abstrakt

Ziel der Arbeit war es zu beweisen, dass bestimmte radiologische Befunde und klinisch-radiologische Scores wertvolle Informationen liefern können, um den klinischen Verlauf und die Prognose neuroendokriner Neoplasien (NEN) besser zu verstehen.

Mesenterialfibrose (MF) ist ein radiologisch pathognomonisches Zeichen für Mitteldarm-NEN. In der Publikation 1 wurde eine potenzielle Beziehung zwischen MF und Karzinoid-Syndrom, 5-Hydroxyindolessigsäure (5-HIAA) im Urin und Karzinoid-Herzkrankheit (CHD) untersucht. Die bildgebenden Eigenschaften von lymphatischen und hepatischen Metastasen bei Diagnose, 5-HIAA, Funktionalität und Entwicklung von CHD wurden aus einer Kohorte von 81 Patienten analysiert. Unabhängige Prädiktoren für MF waren $5\text{-HIAA} \geq 395 \mu\text{mol/Tag}$, Alter und größte lymphatische Metastase $\geq 24 \text{ mm}$ ($p < 0,05$). MF war in funktionellen Mitteldarm-NEN mit einer verkürzten Zeit bis zur Entwicklung von CHD assoziiert ($p < 0,05$). Eine Assoziation zwischen MF und 5HIAA wurde gefunden, die auf einen verknüpften pathophysiologischen Mechanismus hinweist, der bei endokardialen Fibröse in CHD ähnlich sein könnte.

In der Publikation 2 nahm Charité an einer multizentrischen Studie teil, in der die Kombination mehrerer Risikofaktoren analysiert wurde, um die Progredienz bei gastroentero-pankreatischem NEN vorherzusagen. Eine multivariate Analyse auf Progredienz wurde in einer Kohorte von 256 Patienten durchgeführt. Unabhängige Risikofaktoren für die Progredienz waren der Proliferationsindex Ki67, die radiologisch bewertete Belastung des Lebertumors und das Vorhandensein von extraabdominalen Metastasen. Es wurde eine Risiko-Score-Formel erhalten, die eine überlegene Genauigkeit zur Vorhersage der Progredienz im Vergleich zu einem auf Ki67 basierenden Bewertungssystem zeigte.

Ziel der Publikation 3 war es klinischen Anzeichen und Computertomographie (CT) Befunde bei Everolimus-induzierter Pneumonitis zu korrelieren. 18 Patienten, aus einer Kohorte von 90 NEN-Patienten, hatten Pneumonitis. Klinische Anzeichen einer Pneumonitis wurden bewertet und Lungenfunktionstests (PFT) wurden analysiert, falls verfügbar. CT-Bilder wurden basierend auf der Schwere der interstitiellen Lungenerkrankung (ILE), dem Gesamtausmaß der Pneumonitis (PnE) und dem Vorhandensein typischer Lungentrübungsmuster analysiert. Es gab keine signifikante Korrelation zwischen dem symptomatischen Score oder dem PFT- und ILD-Score oder dem PnE. Das kryptogen organisierende Lungentzündungsmuster hatte signifikant

niedrigere symptomatische Score als bei anderen Trübungsmustern ($p < 0,05$). Asymptomatische Patienten mit spezifischen Pneumonitis-CT-Befunden sollten engmaschig überwacht werden, damit die Behandlung rechtzeitig eingeleitet werden kann.

Zusammenfassend war die radiologische Beurteilung der Leber- oder Lungenerkrankung ein wertvolles Instrument zur Analyse von NEN. CT-Lungenbefunde zeigten keine klinische Korrelation bei Everolimus-induzierter Pneumonitis. Die Belastung durch Lebertumoren erwies sich sowohl für die NEN-Prognose als auch für die MF als relevanter Faktor. MF und 5HIAA können eine wichtige Rolle in der Pathophysiologie von MF spielen.

Abstract

The aim of this study was to prove that specific radiological findings and clinical-radiological scores can give physicians valuable information in order to better understand the clinical course and prognosis of neuroendocrine neoplasms (NEN).

Mesenteric fibrosis (MF) is a radiological pathognomonic sign of midgut NEN. In Publication 1 a potential relationship of MF with carcinoid syndrome, urinary 5-hydroxyindoleacetic acid (5-HIAA), and carcinoid heart disease (CHD) was assessed. Imaging characteristics of lymphatic and hepatic metastases at diagnosis, 5-HIAA, functionality, and development of CHD were analyzed from a cohort of 81 patients. Independent predictors of MF were 5-HIAA ≥ 395 $\mu\text{mol/day}$, age, and largest lymphatic metastasis ≥ 24 mm ($p < 0.05$). MF was associated with decreased time to development of CHD in functional midgut NENs ($p < 0.05$). An association between MF and 5HIAA was found which suggests a linked pathophysiological mechanism, which might be similar to that of endocardial fibrosis in CHD.

In Publication 2 Charité was part of a multicenter study which analyzed the combination of several risk factors to predict progression of disease (PD) in gastro-entero-pancreatic NEN. Multivariate analysis for PD was performed in a cohort of 256 patients. Independent risk factors for PD were proliferative index Ki67, radiologically assessed hepatic tumor burden, and presence of extra-abdominal metastases. A risk score formula was obtained which showed a superior accuracy to predict PD compared with grading system based in Ki67.

The purpose in Publication 3 was to evaluate the correlation between clinical signs and computed tomography (CT) findings in everolimus-induced pneumonitis. From a cohort of 90 NEN patients 18 had pneumonitis. Clinical signs of pneumonitis were scored and pulmonary function tests (PFT) were evaluated if available. CT images were analyzed based on the severity of interstitial lung disease (ILD), the overall pneumonitis extent (PnE), and regarding presence of typical lung opacification patterns. There was no significant correlation between symptomatic score or PFT and ILD score or PnE. Cryptogenic organizing pneumonia pattern had significantly lower symptomatic scores than in case of other opacification patterns ($p < 0.05$). Asymptomatic patients with specific pneumonitis CT findings should be closely monitored so that treatment can be timely initiated.

In conclusion, radiological assessment of liver or lung affection were valuable tools in analyzing NEN. CT lung findings showed no clinical correlation in everolimus-induced pneumonitis. Hepatic tumor burden proved to be a relevant factor both for NEN prognosis and MF. MF and 5HIAA may play an important role in the pathophysiology of MF.

Introduction

Neuroendocrine neoplasms (NEN) are rare and heterogeneous group of malignancies that can arise from neuroendocrine cells of various locations mostly in gastrointestinal tract and pancreas as well as lung. NEN are characterized by their ability to produce peptides that cause characteristic hormonal syndromes. In recent decades, the incidence of NEN has steadily increased. Most are more indolent than other epithelial malignancies; however, they can be aggressive and resistant to therapy (1). Due to the slow-growing nature of these tumors and the lack of early symptoms, most cases are diagnosed at advanced stages, when curative treatment options are no longer available. We hypothesized that specific radiological findings (MF, hepatic tumor burden and lung affection) as well as scores (clinical and radiological) can give physicians valuable information in order to better understand the clinical course and prognosis of NEN.

NEN with embryonic origin in midgut (small bowel, appendix and ascending colon) are the most frequently associated with carcinoid syndrome, which is characterized by flushing, diarrhea, and potential development of progressive right-sided endocardial fibrosis with carcinoid heart disease (CHD) (2). The main mediator of carcinoid syndrome is serotonin and 5-Hydroxyindoleacetic acid (5-HIAA) is the main metabolite of serotonin. Mesenteric fibrosis (MF) due to desmoplastic reaction surrounding a lymphatic metastasis in the mesentery is a radiological pathognomonic sign of midgut NEN (3) but its pathophysiology is poorly understood. It can cause gastrointestinal complications, such as ischemia or inoperability of the primary tumor. The relationship between CHD and serotonin is supported by various studies (4) but the association between serotonin and MF has not been studied in depth. The purpose of Publication 1 was to investigate potential relationships between MF and clinical and radiological factors of midgut NEN in order to better understand the pathogenesis and clinical significance of this particular finding.

Several factors such as grading expressed by proliferative Ki67 index, disease staging, presence and extension of distant metastases and primary tumor site are already known factors that affect clinical outcome of gastro-entero-pancreatic (GEP) NEN (5, 6). The prognostic role of the combination of the above-mentioned risk factors has not been investigated. Moreover, the extension of liver metastases assessed by radiological examinations has only been arbitrarily stratified in previous studies (7). Publication 2

aimed at identifying factors that can predict poor clinical outcome and combine them to obtain a risk score to quantify the risk of progression. An additional goal was to standardize stratification of hepatic tumor burden. Due to the low incidence of NEN this project was designed as a multicenter study.

Everolimus, a mammalian target of rapamycin (mTOR)-inhibitor, is approved for the treatment of lung and metastatic GEP NENs and has been associated with improved progression-free survival (PFS) (8, 9). Drug-related pneumonitis occurs as a major adverse event in mTOR inhibitor therapy and is recognized as a class-effect toxicity which induces lung injury (10). The occurrence of pneumonitis as an adverse drug reaction is commonly treated by corticosteroids but dose reduction and even termination of everolimus treatment can become necessary (11). The diagnosis of pneumonitis is strongly based on computed tomography (CT). Little is known about severity of CT findings regarding the extent of lung involvement and disease pattern in relation to clinical signs. The study of the significance of these CT-findings is decisive to optimize patient management. Therefore, the purpose of Publication 3 was to analyze the CT findings of pneumonitis in relation to clinical severity in NEN patients treated with everolimus.

Methods

Mesenteric Fibrosis

The Charité database was searched for patients with pathologically proven NEN with primary site in the midgut treated at our center during the period 2008 through 2014. In order to better understand the factors implicated in the development of MF we included only patients with the potential to develop MF and that is presence of at least one lymphatic metastasis in the mesentery. Our final cohort consisted of 81 patients.

Imaging features were assessed at the time of initial midgut NEN diagnosis by means of CT or magnetic resonance imaging (MRI). MF was defined as an enhancing spiculated soft-tissue mass with fibrotic bands radiating outward in the mesenteric fat in a stellate pattern around a lymph node metastasis (3).

Other features of mesenteric nodal metastases were recorded: number, longest diameter, presence of calcification, and presence of vascular encasement. We assessed the hepatic tumor involvement as an estimated percentage of the total liver volume by means of a visual semiquantitative evaluation. Additional hepatic metastases (HM) characteristics were recorded such as number of liver lesions, longest diameter, and presence of hypervascularity.

Midgut NEN were considered clinically functional when at least one key symptom of the carcinoid syndrome (i.e., diarrhea or flushing) was present in addition to elevated 5-HIAA ($\geq 47 \mu\text{mol/d}$). Functional patients were followed up with transthoracic echocardiography in order to detect development of CHD.

Risk score

A retrospective analysis on institutional databases from five participating international centers (Rome, Milan, Berlin, Marburg, and Graz) was performed. The study included 283 consecutive patients with sporadic stage IV GEP-NENs diagnosed from 2000 to 2015. 42 patients from the Charité database were included.

Functional status, primary tumor characteristics (location, size, resection, grading) and presence of extra abdominal metastases were recorded. Hepatic tumor burden was calculated visually as in Publication 1 and patients were classified into three different

categories: no liver metastases present or metastatic liver involvement <25%; metastatic liver involvement 25%–50%; metastatic liver involvement >50%.

The primary end point considered was progression-free survival (PFS), which was defined as the interval between diagnosis of stage IV GEP-NENs and time of progressive disease (PD) or patient death.

Pneumonitis

The Charité database was searched for patients with advanced pathologically confirmed NEN treated at our center with everolimus before 2014. A total of 90 patients were included in this retrospective study.

All included patients received a CT of the chest prior to the initiation of everolimus therapy and every 12 weeks until the termination of therapy or last follow-up. All patients were physically examined on the day the CT scans were performed. Clinical signs were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (12). We quantified the clinical signs with a scoring system combining cough and dyspnea. This symptomatic score resembled the sum of cough grading (ranging from 1 to 3) and dyspnea grading (ranging from 1 to 5). The score therefore ranged from 0 (asymptomatic) to a maximum of 8 points.

All chest CT scans were evaluated for the presence of lung abnormalities suspicious for drug-related pneumonitis. In order to quantify these findings, we used a CT score proposed by Ichikado et al (13) which has been applied to interstitial pneumonias. Our findings were graded on a scale of 1 to 5: 1 = normal lung attenuation; 2 = ground-glass opacities; 3 = consolidation; 4 = ground-glass opacities with associated reticulation and traction bronchiectasis and/or bronchioloectasis; 5 = consolidation with and bronchioloectasis. Each lung was divided in upper, middle and lower zones. Pulmonary extent was visually assessed for each finding to the nearest 5% in each zone. The overall percentage of each finding was obtained by averaging the values of all lung zones. The total score, defined as Interstitial Lung Disease (ILD) score, was calculated by the sum of multiplying the of each finding and the corresponding grade. The highest possible ILD score was therefore 500 (100% of lung parenchyma with grade 5 findings) and the lowest possible score was 100 (normal attenuation of the whole lung). Additionally, we calculated the global radiological affection of both lungs, defined as

pneumonitis extent (PnE), by averaging the percentage of all the 6 lung zones. The highest possible PnE was 100% (entire lung) and the lowest PnE was 0%.

Patterns of pneumonitis were classified as previously described by Nishino et al. (14) as: 1) usual interstitial pneumonia pattern; 2) nonspecific interstitial pneumonia (NSIP) pattern; 3) cryptogenic organizing pneumonia (COP) pattern; 4) acute interstitial pneumonia/acute respiratory distress syndrome pattern; 5) hypersensitivity pneumonitis pattern, and 6) not applicable. If PFT were available the diffusion capacity for carbon monoxide divided by the alveolar volume (DLCO/VA) was recorded and defined as pathologically low if $\leq 80\%$.

Imaging analysis

Two experienced radiologists from our center reviewed all images retrospectively in consensus for Publication 1 and 3. One experienced radiologist reviewed all images retrospectively for Publication 2.

Statistical Analysis

Statistical analysis was performed using SPSS (version 22 for Windows: IBM Corp., Armonk, USA) for Publication 1 and 2 and Medcalc 16 (Belgium, www.medcalc.org) for Publication 3. Results were considered statistically significant when $p < 0.05$.

Results

Mesenteric Fibrosis

Of 81 patients included in our study, MF was present in 44 (54%) (Fig. 1). Mesenteric ischemia was present at diagnosis in 2 patients with MF. The presence of MF was more frequently associated with mesenteric vessel encasement (100% vs. 46% without MF; $p < 0.001$), presence of hepatic metastases (91% vs. 62%; $p = 0.002$), larger hepatic tumor burden (15% vs 5%; $p = 0.001$), and functionality (86% vs 43%; $p < 0.001$). Distant non-hepatic metastases were significantly more common among patients with MF (39% vs. 14% of patients; $p < 0.011$).

Multivariate analysis revealed 5-HIAA ≥ 395 $\mu\text{mol/d}$ ($p = 0.020$), age ($p = 0.013$), and largest lymphatic metastasis ≥ 24 mm ($p = 0.009$) as independent predictors of MF, while functionality ($p = 0.098$) and development of CHD ($p = 0.070$) showed a tendency towards significance.

As CHD only develops with functional NET, we performed a subgroup analysis in this risk group ($n = 48$). MF was associated with decreased time to development of CHD in functional midgut NET ($p = 0.043$). In multivariate analysis, 5-HIAA ≥ 501 $\mu\text{mol/d}$ and hepatic tumor burden $\geq 25\%$ were confirmed to be independent risk factors for CHD, whereas MF was excluded from the model due to loss of statistical significance.

Risk score

The median PFS from the cohort of 283 patients was 18 months. Proliferative index Ki67, the proportion of liver involvement (Fig. 2), and the presence of distant extra-abdominal metastases were confirmed to be independent risk factors for PD. The b coefficients of these variables were used to generate a risk score as follows: $(0.025 \times \text{Ki67 value}) + [(0 \text{ if no liver metastases present or liver involvement } < 25\%) \text{ OR } (0.405 \text{ if liver involvement } 25\% - 50\%) \text{ OR } (0.462 \text{ if liver involvement } > 50\%)] + [(0 \text{ if extra-abdominal metastases absent}) \text{ OR } (0.528 \text{ if extra-abdominal metastases present})]$. Overall, the risk score model ability to discriminate between patients who did and who did not experience PD was good, with an area under the curve (AUC) being 0.705. This accuracy level was higher than that of the G grading system (AUC of 0.622) which is based in proliferative index Ki67.

We identified three different groups (low, intermediate and high-risk) according to their risk score with median PFS being 26 months, 19 months, and 12 months, respectively ($p < .0001$).

Pneumonitis

Pneumonitis was diagnosed in 18 patients (20%) of a total of 90. No patient characteristics appeared to be associated with the occurrence of pneumonitis. From these 18 patients, 10 were asymptomatic. All 18 patients had chest CT scans before the initiation of treatment for pneumonitis. There was no statistically significant correlation between our symptomatic score and PnE ($p=0.273$) and ILD score ($p=0.288$). Pulmonary functions test showed additionally no statistically significant correlations. The most frequent pattern was cryptogenic organized pneumonia (COP) pattern ($n=14$) (Fig. 3). Its symptomatic scores were significantly lower ($p=0.035$) than in case of the other patterns. There was no asymptomatic patient with a non-COP pattern.

In the follow-up analysis, we could identify four different clinical courses considering dedicated therapy for pneumonitis (everolimus dose modification and / or corticosteroids): A. Asymptomatic patients with prolonged CT findings; B. Symptomatic patients with rapid regression of symptoms and CT findings; C. Symptomatic patients with rapid regression of symptoms however persistence of CT findings; D. Delayed onset of symptoms and prolonged recovery of clinical signs and CT findings.

Discussion

For the majority of patients with NEN, lifelong tumor imaging is necessary every three to nine months (15). Our project demonstrates that a better knowledge of specific radiologic findings of NEN and the use of clinical-radiological scores could be beneficial in understanding NEN.

MF is the hallmark of midgut NEN. However, it does not affect, by far, all patients with mesenteric lymph node metastases. In Publication 1, the fibrotic reaction always surrounded the largest mesenteric nodal metastases. A greater diameter of the largest nodal metastases, compared to patients without MF, was a predictive factor for MF. Nevertheless, in few cases, very large nodal metastases were also seen in patients without MF. Therefore, size alone is not the (only) decisive factor in MF development. Vessel encasement was always associated with MF and consequently abdominal pain was more often present with MF. Additional radiological features associated with MF were calcification and a larger hepatic tumor burden. We established a potential link between MF and higher values of 5-HIAA. Two prior clinical studies do not fully support the link between MF and functional tumors (16, 17) but various limitations were found. Although serotonin maybe one of the triggers (3) the mechanisms of fibrosis remain complex as patients without carcinoid syndrome can develop severe desmoplasia. A severe complication of functional NEN is the development of CHD, which typically occurs in patients with severe and long-standing elevations of circulating serotonin (18). From the functional patients in our cohort in Publication 1, 45% of them developed CHD. The criterion MF separated the time-to-event curves with MF being an indicator of lower CHD-free survival rate ($p=0.043$), so that a link between MF and CHD can be hypothesized. However, in the multivariate analysis, only hepatic tumor burden $\geq 25\%$ and 5-HIAA levels $\geq 501 \mu\text{mol/d}$ were independent risk factors for development of CHD. The association of MF with elevated levels of 5-HIAA and higher hepatic tumor burden is potentially indicative of a causal relationship, either via the systemic circulation or due to local secretion of serotonin. Furthermore, MF and CHD seem to have a potential link, suggesting that they share a similar pathogenesis.

The study in Publication 2 showed that, when diagnosing stage IV GEP- NENs, it is possible to obtain an easy-to-use tool that is effective in stratifying the risk of PD. This risk score was based on data that are usually available, such as Ki67 and radiological disease extension (presence of extra-abdominal metastases and hepatic tumor burden).

The liver (85%) is the most common site for metastases in NEN (5). Hepatic liver burden has been increasingly used because of its potential importance as a prognostic factor (19), but it has not been stratified so far. Other studies have arbitrarily proposed 10 or 25% to define limited disease (19, 20). We demonstrated that the three groups of hepatic tumor burden (0-25; 25 to 50, >50%) are statistically valid besides easy to remember. In Publication 1 stage IV was not a specific inclusion criterion and therefore the median value of hepatic tumor burden in patients with hepatic metastases was low (10%). Applying the stratified values as in Publication 2 did not seem useful in this case and was used as a linear variable. All 48 functional patients in Publication 1 which received follow up for CHD were stage IV NEN. In this group 25% proved to be a good stratification value for hepatic tumor burden as it showed to be an independent prognostic factor for CHD.

Pneumonitis is a well-known adverse effect of everolimus in metastatic renal cell carcinoma but few studies have investigated its presence when treating neuroendocrine tumors. Incidence of pneumonitis in Publication 3 was 20% and COP pattern was the most frequently observed which are consistent with a previous study by Nishino et al (14). Dyspnea and dry cough are the most common observed clinical signs associated to pneumonitis (21). Dyspnea is a severe symptom therefore it received a higher value in our symptomatic score. We calculated as in Publication 1 and 2 the global radiological affection of an organ (from 0 to 100%), in this case the lung (pneumonitis extent). The study showed that pneumonitis extent or grade of pulmonary changes (ILD score) in CT do not significantly correlate with clinical signs or PFT. Only with distinct pattern analysis could we show that the common COP pattern is significantly more often found in asymptomatic patients than a non-COP pattern. We identified four different types of clinical courses in our cohort. The most interesting groups consist of asymptomatic patients with CT findings, which can either show a prolonged asymptomatic course with persistent CT findings or with the development of symptoms within the next three months. If clinical signs occurred, these patients showed longer-term symptoms and CT findings even under therapy.

The results of all publications were limited because of its retrospective design and therefore prospective trials are needed to confirm our findings. In Publication 1 and 3 results were also limited due to the small cohort. In Publication 1 MF is a widely accepted imaging criterion but it is not confirmed histopathologically.

In conclusion, we found a link between MF and 5HIAA which suggests a linked pathophysiological mechanism, which might be similar to that of endocardial fibrosis.

Hepatic tumor burden proved to be a relevant factor both for NEN prognosis and MF. GEP NEN risk score could help physicians select the patients in whom an early aggressive therapeutic approach is recommended as well as to plan an individualized follow-up program.

The severity of CT lung findings showed no clinical correlation in everolimus-induced pneumonitis. Asymptomatic patients should be closely monitored so that treatment can be timely initiated. Distinct CT pattern analysis may help in the assessment of clinical severity.

Finally, it may be concluded that radiological assessment of liver or lung affection were valuable tools in analyzing NEN. The future in radiology will imply artificial intelligence which can help calculate easily disease extent and could be integrated in daily radiological reports. Future development of additional radiological-clinical scores could be a useful additional tool in the treatment of NEN.

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Statutory Declaration

“I, Víctor Julio Rodríguez Laval, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic: “Neuroendocrine Neoplasms: Radiologic-Clinical Correlation / Neuroendokrine Neoplasien: Radiologische und Klinische Korrelation” independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date

Signature

Declaration of selected publications

Víctor Julio Rodríguez Laval contributed the following to the below listed publications:

Publication 1:

Rodríguez Laval V, Pavel M, Steffen IG, Baur AD, Dilz LM, Fischer C, Detjen K, Prasad V, Pascher A, Geisel D, Denecke T. Mesenteric Fibrosis in Midgut Neuroendocrine Tumors: Functionality and Radiological Features. *Neuroendocrinology*. 2018;106(2):139-147.

Contribution:

Project conception and design under guidance of Prof. Denecke, collection of data, evaluation of imaging tests (CTs and MRIs) of all patients, statistical data analysis with the help of statistics program SPSS under the supervision of the statistician and co-author Ingo G. Steffen, creation of all figures and all tables, first and final draft manuscript writing, final approval of manuscript after corrections received from the co-authors, correspondence throughout the peer review process.

Publication 2:

Panzuto F, Merola E, Pavel ME, Rinke A, Kump P, Partelli S, Rinzivillo M, Rodriguez-Laval V, Pape UF, Lipp R, Gress T, Wiedenmann B, Falconi M, Delle Fave G. Stage IV Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: A Risk Score to Predict Clinical Outcome. *Oncologist*. 2017 Apr;22(4):409-415.

Contribution:

Workgroup with Dr. Merola in order to investigate new radiological risk factors, collection of data, evaluation of imaging tests (CTs and MRIs) from all patients from the Charité, proposal of manuscript corrections before final approval.

Publication 3:

Fehrenbach U, Rodríguez-Laval V, Jann H, Fernández CMP, Pavel M, Denecke T. Everolimus-induced pneumonitis in neuroendocrine neoplasms: correlation of CT findings and clinical signs. Acta Radiol. 2020 Aug 20:284185120950100. Epub ahead of print.

Contribution:

Project conception and design under guidance of Prof. Denecke and within a workgroup with Dr. Fehrenbach, collection of data, evaluation of imaging tests (CTs) of all patients, statistical data analysis in cooperation with Dr. Fehrenbach with the help of statistics program SPSS, first draft manuscript writing, proposal of manuscript corrections before final approval.

Signature, date and stamp of first supervising university professor / lecturer

Signature of doctoral candidate

Selected publications

Publication 1:

Rodríguez Laval V, Pavel M, Steffen IG, Baur AD, Dilz LM, Fischer C, Detjen K, Prasad V, Pascher A, Geisel D, Denecke T.

Mesenteric Fibrosis in Midgut Neuroendocrine Tumors: Functionality and Radiological Features.

Neuroendocrinology. 2018;106(2):139-147.

DOI: <https://doi.org/10.1159/000474941>

Publication 2:

Panzuto F, Merola E, Pavel ME, Rinke A, Kump P, Partelli S, Rinzivillo M, Rodriguez-Laval V, Pape UF, Lipp R, Gress T, Wiedenmann B, Falconi M, Delle Fave G.

Stage IV Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: A Risk Score to Predict Clinical Outcome.

Oncologist. 2017 Apr;22(4):409-415.

DOI: <https://doi.org/10.1634/theoncologist.2016-0351>

Publication 3:

Fehrenbach U, Rodríguez-Laval V, Jann H, Fernández CMP, Pavel M, Denecke T.
Everolimus-induced pneumonitis in neuroendocrine neoplasms: correlation of CT
findings and clinical signs.

Acta Radiol. 2020 Aug 20:284185120950100. Epub ahead of print.

DOI: <https://doi.org/10.1177/0284185120950100>

Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection

Publications

Articles

1.

Panzuto F, Merola E, Pavel ME, Rinke A, Kump P, Partelli S, Rinzivillo M, Rodríguez-Laval V, Pape UF, Lipp R, Gress T, Wiedenmann B, Falconi M, Delle Fave G. Stage IV Gastro-Entero-Pancreatic Neuroendocrine Neoplasms: A Risk Score to Predict Clinical Outcome. *Oncologist*. 2017 Apr;22(4):409-415.

Impact factor: 5,306 (2017)

2.

Rodríguez Laval V, Pavel M, Steffen IG, Baur AD, Dilz LM, Fischer C, Detjen K, Prasad V, Pascher A, Geisel D, Denecke T. Mesenteric Fibrosis in Midgut Neuroendocrine Tumors: Functionality and Radiological Features. *Neuroendocrinology*.

2018;106(2):139-147.

Impact factor: 6,804 (2018)

3.

Fehrenbach U, Rodríguez-Laval V, Jann H, Fernández CMP, Pavel M, Denecke T. Everolimus-induced pneumonitis in neuroendocrine neoplasms: correlation of CT findings and clinical signs. *Acta Radiol*. 2020 Aug 20:284185120950100. *Acta Radiol*. 2020 Aug 20:284185120950100. Epub ahead of print.

Impact factor: 1,635 (2019)

4.

Pape UF, Kasper S, Meiler J, Sinn M, Vogel A, Müller L, Burkhard O, Caca K, Heeg S, Büchner-Steudel P, Rodríguez-Laval V, Kühl AA, Arsenic R, Jansen H, Treasure P, Utku N. Efficacy and Safety of CAP7.1 as Second-Line Treatment for Advanced Biliary Tract Cancers: Data from a Randomised Phase II Study. *Cancers*. 2020 Oct 27;12(11):E3149.

Impact factor: 6,126 (2019)

International Posters and Presentations

1.

Rodríguez-Laval V, Muñoz Hernández P, Gómez León N. Role of Imaging in Tumoral Periosteal Reaction: A Pictorial Review with Pathological Correlation. Educational exhibit. Radiological Society of North America (RSNA) Scientific Assembly and Annual Meeting, Chicago, USA, November 29-December 5 2020.

2.

Rodríguez Laval V, Pavel M, Steffen I, Wiedenmann B, Denecke T. Midgut neuroendocrine tumours: is there a link between mesenteric fibrosis and carcinoid heart disease? Oral presentation. European Congress of Radiology (ECR), Vienna, Austria, March 2-6 2016.

3.

Rodríguez Laval V, Tischer E, Pavel M, Wiedenmann B, Hamm B, Denecke T. Small Bowel Neuroendocrine Tumors (NET): Relationship Between Radiologic Features, Functionality and Ki-67 Classification. Scientific exhibit. European Neuroendocrine Tumor Society (ENETS) Conference, Barcelona, March 11-13 2015.

4.

Rodríguez Laval V, Herrera I, Meléndez B, Mollejo M, García Benassi. Assessment of MR and biological prognostic factors in Glioblastoma multiforme. Scientific exhibit. ECR, Vienna, March 7-11 2013.

5.

Rodríguez V, Gómez Moreno A, Herrero Y, Ciampi Dopazo J, Pinto J, Gómez Rodríguez R, Fernández Zapardiel S, Artiles Valle V, Céspedes Mas M, Vargas Orozco I, Hernández Guilabert P. Immediate follow-up imaging findings and complications after locoregional treatment for hepatocellular carcinoma. Educational exhibit. RSNA Scientific Assembly and Annual Meeting, Chicago, USA, December 1-6 2013.

6.

Rodríguez Laval V, Caracela Zeballos CR, Fernández S, Herrero Gómez Y, Artiles V, Céspedes M. Efficacy of ADC map in the evaluation of patients with cervical cancer after non-surgical treatment with pathological findings correlation. Scientific exhibit. ECR, Vienna, March 1-5 2012.

7.

Rodríguez Laval V, Herrera Herrera I, Reyes A, Caracela Zeballos CR. Non-traumatic head and neck pathologies: what every radiologist should know. Oral presentation. Congreso de la Sociedad Española de Radiología Médica (SERAM), Granada, Spain, May 25-28 2012.

8.

Rodríguez V, Herrera I, García Benassi J, González Gutiérrez R, Capilla E, Vidal González J, Reyes Ortiz A, Sánchez Camacho P, Fernández Taranilla M. Imaging Findings of Hodgkin and Non-Hodgkin Lymphoma in the Head and Neck. Educational exhibit. RSNA Scientific Assembly and Annual Meeting, Chicago, November 25-30 2012.

9.

Rodríguez V, Herrera I, García Benassi J, González Gutiérrez R, Capilla E, Caracela Zeballos C, Vargas Orozco I, Moreno De La Presa R, González-Tovar R. Diagnostic Imaging in Non-traumatic Head and Neck Emergencies. Educational exhibit. RSNA Scientific Assembly and Annual Meeting, Chicago, November 25-30 2012.

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This work is dedicated to Blanca Romero Calvo, rest in peace.