

BiblioGETNE

Nº5 - Marzo 2022

ÍNDICE

Getne Academy

Introducción

Artículos y comentarios de cada especialidad
Caso clínico

Introducción

GETNE ACADEMY tiene el placer de enviar el quinto número de **BiblioGETNE**, la newsletter dirigida a todos los socios de GETNE de manera trimestral y en la que se recogen diversos artículos científicos, seleccionados desde cada una de las especialidades que abarca actualmente GETNE ACADEMY: Oncología Médica, Cirugía General, Medicina Nuclear, Endocrinología y Anatomía Patológica. Al final de cada artículo, se realiza un breve comentario.

En este número se han unido a la newsletter las Dras. Montse Negre y Lavinia Benini, que aportarán al documento sus comentarios sobre un artículo de investigación y un caso clínico, respectivamente.

Esperamos que la información sea de vuestro interés.

Un cordial saludo,

El equipo de GETNE ACADEMY

getne.academy@getne.org
getne@getne.org
[@GrupoGetne](https://twitter.com/GrupoGetne)

MGMT expression predicts response to temozolomide in pancreatic neuroendocrine tumors

J Cros^{1,2,*}, O Hentic^{3,*}, V Rebours^{2,3}, M Zappa⁴, N Gille¹, N Theou-Anton⁵, D Vernerey⁶, F Maire³, P Lévy^{2,3}, P Bedossa^{1,2}, V Paradis^{1,2}, P Hammel^{2,7}, P Ruszniewski^{2,3} and A Couvelard^{2,8}

¹Department of Pathology, AP-HP, DHU UNITY, Beaujon University Hospital, Clichy, France

²U1149 – University Paris Diderot, Paris, France

³Department of Gastroenterology and Pancreatology, AP-HP, DHU UNITY, Beaujon University Hospital, Clichy, France

⁴Department of Radiology, AP-HP, DHU UNITY, Beaujon Hospital, Clichy, France

⁵Department of Somatic Genetic, AP-HP, DHU UNITY, Bichat University Hospital, Paris, France

⁶Methodology and Quality of Life in Oncology Unit (EA 3181), University Hospital of Besançon, Besançon, France

⁷Department of Digestive Oncology, AP-HP, DHU UNITY, Beaujon University Hospital, Clichy, France

⁸Department of Pathology, AP-HP, DHU UNITY, Bichat University Hospital, Paris, France

*(J Cros and O Hentic contributed equally to this work)

Correspondence
should be addressed
to A Couvelard

Email

anne.couvelard@bch.aphp.fr

Abstract

Temozolomide (TEM) showed encouraging results in well-differentiated pancreatic neuroendocrine tumors (WDPNETs). Low *O*⁶-methylguanine-DNA methyltransferase (MGMT) expression and *MGMT* promoter methylation within tumors correlate with a better outcome under TEM-based chemotherapy in glioblastoma. We aimed to assess whether MGMT expression and *MGMT* promoter methylation could help predict the efficacy of TEM-based chemotherapy in patients with WDPNET. Consecutive patients with progressive WDPNET and/or liver involvement over 50% who received TEM between 2006 and 2012 were retrospectively studied. Tumor response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines. Nuclear expression of MGMT was assessed by immunochemistry (H-score, 0–300) and *MGMT* promoter methylation by pyrosequencing. Forty-three patients (21 men, 58 years (27–84)) with grade 1 WDPNET (*n*=6) or 2 (*n*=36) were analyzed. Objective response, stable disease, and progression rates were seen in 17 patients (39.5%), 18 patients (41.9%), and 8 patients (18.6%), respectively. Low MGMT expression (≤ 50) was associated with radiological objective response ($P=0.04$) and better progression-free survival (PFS) ($HR=0.35$ (0.15–0.81), $P=0.01$). Disease control rate at 18 months of treatment remained satisfying with an MGMT score up to 100 (74%) but dropped with a higher expression. High *MGMT* promoter methylation was associated with a low MGMT expression and longer PFS ($HR=0.37$ (0.29–1.08), $P=0.05$). Low MGMT score (≤ 50) appears to predict an objective tumor response, whereas an intermediate MGMT score (50–100) seems to be associated with prolonged stable disease.

Key Words

- ▶ temozolomide
- ▶ MGMT
- ▶ pancreatic neuroendocrine tumors
- ▶ methylation

Endocrine-Related Cancer
(2016) 23, 625–633

MGMT expression predicts response to temozolomide in pancreatic neuroendocrine tumors

<https://erc.bioscientifica.com/view/journals/erc/23/8/625.xml>

Comentario:

La enzima O6-metilguanina-metiltransferasa (MGMT) dificulta la acción citotóxica de la temozolomida al facilitar la acción del sistema de reparación del DNA y estabilizando el material genético. Sobre este razonamiento, la metilación del promotor del gen de la MGMT y los bajos niveles de expresión supondrían un mejor pronóstico en pacientes tratados con temozolomida.

En esta serie se incluyeron 43 pacientes con tumores neuroendocrinos pancreáticos bien diferenciados tratados con temozolomida ó temozolomida-capecitabina entre 2006 y 2012 en Francia. Se estudiaron los niveles de expresión de MGMT mediante inmunohistoquímica y la metilación del promotor con pirosecuenciación.

Entre los pacientes analizados, se objetivó respuesta parcial en 17 (39.5%) y estabilización en 18 (41.9%). Un bajo nivel de expresión de MGMT (<50) se asoció con respuesta radiológica ($p = 0.04$) y una mejor supervivencia libre de progresión ($p = 0.01$).

Existía una buena correlación entre una elevada metilación del promotor y la baja expresión de MGMT, con relación directa con la PFS ($p = 0.05$).

Este estudio contribuyó al establecimiento de MGMT como un factor predictivo de respuesta a temozolomida, con una determinación sencilla mediante inmunohistoquímica. Actualmente esta determinación se incluye dentro de la batería de biomarcadores recomendados en pacientes con TNE pancreáticos según la última versión de las guías ESMO. No obstante, la falta de evidencia prospectiva y la limitación de alternativas terapéuticas, hacen que todavía no sea un biomarcador del todo implantado en la práctica clínica.



International survey on opinions and use of minimally invasive surgery in small bowel neuroendocrine neoplasms

Enes Kaçmaz ^{a,b}, Anton F. Engelsman ^{a,b}, Willem A. Bemelman ^a, Pieter J. Tanis ^{a,b}, Elisabeth J.M. Nieveen van Dijkum ^{a,b,*}, on behalf of the International Study Group of Small bowel neuroendocrine neoplasm Surgery (ISGSS)

^a Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands

^b Amsterdam Center for Endocrine and Neuroendocrine Tumours, Amsterdam UMC, Amsterdam, the Netherlands

ARTICLE INFO

Article history:

Received 8 October 2021

Received in revised form

25 October 2021

Accepted 8 November 2021

Available online xxx

Keywords:

Neuroendocrine neoplasms

Minimally invasive surgery

Survey

ABSTRACT

Introduction: Although minimally invasive surgery is becoming the standard technique in gastrointestinal surgery, implementation for small bowel neuroendocrine neoplasms (SB-NEN) is lagging behind. The aim of this international survey was to gain insights into attitudes towards minimally invasive surgery for resection of SB-NEN and current practices.

Methods: An anonymous survey was sent to surgeons between February and May 2021 via (neuro) endocrine and colorectal societies worldwide. The survey consisted of questions regarding experience of the surgeon with minimally invasive SB-NEN resection and training.

Results: A total of 58 responses from five societies across 20 countries were included. Forty-one (71%) respondents worked at academic centers. Thirty-seven (64%) practiced colorectal surgery, 24 (41%) endocrine surgery and 45 (78%) had experience in advanced minimally invasive surgery. An open, laparoscopic or robotic approach was preferred by 23 (42%), 24 (44%), and 8 (15%) respondents, respectively. Reasons to opt for a minimally invasive approach were mainly related to peri-operative benefits, while an open approach was preferred for optimal mesenteric lymphadenectomy and tactile feedback. Additional training in minimally invasive SB-NEN resection was welcomed by 29 (52%) respondents. Forty-three (74%) respondents were interested in collaborating in future studies, with a cumulative median (IQR) annual case load of 172 (86–258).

Conclusions: Among respondents, 69% applies minimally invasive surgery for resection of SB-NEN. Arguments for specific operative approaches differ, and insufficient training in advanced laparoscopic techniques seems to be a barrier. Future collaborative studies can provide better insight in selection criteria and optimal technique.

© 2021 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Although minimally invasive surgery has several generally acknowledged applications in the treatment of gastrointestinal malignancies, its use for small bowel neuroendocrine neoplasms (SB-NEN) is not yet widely accepted. This could be explained by the rarity which limits clinical exposure, and the fact that surgeons

treating SB-NEN are not necessarily those with experience in advanced laparoscopic surgery. One of the technical challenges specific for SB-NEN are the nodal metastases, as these often extent to the mesenteric root and are present in more than 80% of patients [1]. Dissection of the superior mesenteric vessels has the risk of bleeding, and there are concerns about inappropriate oncological clearance of all macroscopic tumour if using a minimally invasive approach.

The lacking evidence for minimally invasive SB-NEN resection is probably also related to restricted advice regarding minimally invasive SB-NEN resection by The North American Neuroendocrine Tumor Society and European Neuroendocrine Tumor Society [1,2]. Arguments against a minimally invasive approach are mainly based

* Corresponding author. Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands.

E-mail addresses: e.kacmaz@amsterdamumc.nl (E. Kaçmaz), e.j.nieveenvandijkum@amsterdamumc.nl (E.J.M. Nieveen van Dijkum).

José Luis Muñoz de Nova
Cirugía General
Hospital Universitario de La Princesa

International survey on opinions and use of minimally invasive surgery in small bowel neuroendocrine neoplasms

<https://doi.org/10.1016/j.ejso.2021.11.011>

Comentario:

Dada la controversia existente respecto a la idoneidad del abordaje laparoscópico en los pacientes candidatos a resección radical con intención curativa en los TNE intestinales, los autores plantearon una encuesta dirigida a cirujanos para conocer el grado de implantación del abordaje laparoscópico y los aspectos relacionados con el mismo.

Esta encuesta, que fue distribuida por nuestro grupo, fue contestada por 58 cirujanos de 20 países diferentes, incluida España, que trataban de forma habitual TNE intestinales. El abordaje abierto fue el preferido en el 42% de los casos, mientras que el resto prefería el abordaje mínimamente invasivo (44% laparoscópico y 14% robótico). Existía un importante consenso (>80%) respecto a que el abordaje abierto permitía una mejor palpación del intestino y una mejor linfadenectomía y que el abordaje laparoscópico presentaba un menor dolor postoperatorio. La opinión mayoritaria era que los tumores en los que no había adenopatías centrales y los que no había riesgo de resecciones incompletas eran los mejores candidatos a abordajes mínimamente invasivos.

También queda reflejado el bajo número de casos intervenidos, con 4 cirugías al año por cirujano como valor mediano de los participantes. Esto se considera un claro punto de mejora en la atención de los pacientes, ya que la limitada experiencia constituye una barrera para la implementación de los abordajes mínimamente invasivos en este tipo de pacientes, así como la necesidad de realizar estudios multicéntricos para conocer la eficacia y seguridad de los mismos en el contexto de los TNE.



HHS Public Access

Author manuscript

Eur J Cancer. Author manuscript; available in PMC 2022 March 08.

Published in final edited form as:

Eur J Cancer. 2021 March ; 146: 56–73. doi:10.1016/j.ejca.2021.01.008.

Consensus on Molecular Imaging and Theranostics in Neuroendocrine Neoplasms

Valentina Ambrosini^{*,a,b}, Jolanta Kunikowska^{*,c}, Eric Baudin^d, Lisa Bodei^e, Catherine Bouvier^f, Jaume Capdevila^g, Marta Cremonesi^h, Wouter W de Herderⁱ, Clarisse Dromain^j, Massimo Falconi^k, Melpomeni Fanl^l, Stefano Fanti^{a,b}, Rodney J. Hicks^m, Levent Kabasakalⁿ, Gregory Kaltsas^o, Val Lewington^p, Silvia Minozzi^q, Michela Cinquini^r, Kjell Öberg^s, Wim JG Oyen^t, Dermot O'Toole^u, Marianne Pavel^v, Philippe Ruszniewski^w, Aldo Scarpa^x, Jonathan Strosberg^y, Anders Sundin^z, David Taieb^{aa}, Irene Virgolini^{bb}, Damian Wild^{cc}, Ken Herrmann^{#,dd}, James Yao^{#,ee}

^aIRCCS, Azienda Ospedaliero-Universitaria di Bologna, Italy

^bNuclear Medicine, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Italy

^cNuclear Medicine Department, Medical University of Warsaw, Warsaw, Poland

^dEndocrine Oncolgy Unit, Institut Gustave Roussy, Villejuif Cedex, France

^eMolecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York

^fLeamington Spa, UK

^gMedical Oncology Department, Vall Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain

^hRadiation Research Unit, Istituto Europeo di Oncologia, IRCCS, Milano, Italy

ⁱErasmus MC & Erasmus MC Cancer Center, ENETS Center of Excellence Rotterdam, Rotterdam, The Netherlands

^jLausanne University Hospital, Lausanne, Switzerland

^kPancreas Translational & Research Institute, Scientific Institute San Raffaele Hospital and University Vita-Salute, Milan, Italy

^lDivision of Radiopharmaceutical Chemistry, University Hospital Basel, Basel, Switzerland

Corresponding author Prof Ken Herrmann, Department of Nuclear Medicine, Universitätsklinikum, Essen, Germany, Ken.Herrmann@uk-essen.de, +49-20172383660.

*Joint first authors

#Joint last authors

Contributors

VA, JK, SF, SM, and KH designed the study. SM and MiC performed the search, extracted data from retrieved studies, and measured consensus across Delphi rounds. VA, JK, SF, RJH, WO, and KH wrote the paper. VA, EB, LB, JC, MC, WDH, CD, MaF, MeF, RJH, LK, GK, VL, KÖ, DO, MP, PR, ASc, JS, ASu, DT, IV, DW, and JY, were all members of the expert panel, designed the study, contributed to the content of the study, and reviewed the paper. CB contributed the patients' perspective.

Declaration of interests

EB, CB, SM, MiC, MC, LK, GK, KO, WO, ASc, ASu, and IV declare no competing interests.

Montserrat Negre
Medicina Nuclear
Hospital Universitari de Girona Dr. Josep Trueta

**Consensus on Molecular Imaging and Theranostics in
Neuroendocrine Neoplasms**

<https://doi.org/10.1016/j.ejca.2021.01.008>

Comentario:

El artículo expone los resultados del trabajo realizado por el equipo multidisciplinario de ponentes expertos en imagen molecular y teragnóstico en los tumores neuroendocrinos (EANM Focus 3, Atenas enero del 2020).

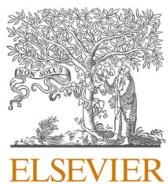
La terapia con péptidos análogos de la somatostatina marcados con radionucleidos (PRRT, por sus siglas en inglés) ha demostrado ser uno de los mayores avances en el manejo terapéutico de los TNE, sobre la base de una correcta selección de los pacientes candidatos estudiados con técnicas de imagen con análogos de la somatostatina (estudio NETTER-1). Aunque cada vez más centros ya disponen de las técnicas diagnósticas y de terapia más avanzadas (⁶⁸Ga-SA PET/TC; ¹⁷⁷Lu-PRRT), existen muchas diferencias en el manejo clínico de los pacientes en los distintos países. Por este motivo y para estandarizar y mejorar el manejo de los pacientes con TNE, la EANM promovió un evento para integrar el conocimiento de la Medicina Nuclear con las otras especialidades involucradas. El objetivo no fue replicar las guías, sino crear un entorno multidisciplinario de expertos internacionales en NEN, reclutados en estrecha colaboración con ENETS, para abordar problemas no resueltos en el manejo y el teragnóstico de los NEN y desarrollar declaraciones de consenso que se pudiesen aplicar a la práctica clínica en todo el mundo. Se escogieron 24 expertos de todo el mundo, según su experiencia y publicaciones sobre el tema (especialistas en medicina nuclear, endocrinología, oncología médica, cirugía, radiofarmacia, gastroenterología, anatomía patológica y radiología). Sobre la base de una búsqueda bibliográfica, se escogieron diversos temas y se desarrollaron unos cuestionarios aplicando el método Delphy modificado. Los 5 temas escogidos fueron: imagen en NEN, imagen y terapia en feocromocitoma y paraganglioma (PPGL), PRRT de los TNE, valoración de respuesta/seguimiento y perspectivas de futuro

Los principales consensos a los que se llegaron fueron:

- Uso de la PRRT en segunda línea para TNE G1, si hay suficiente captación en el estudio con análogos de la somatostatina (Krenning modificado de 3 o 4) en todas las lesiones.
- Consideración de PRRT en pacientes con TNE GEP en la primera progresión de la enfermedad si todas las lesiones positivas son coincidentes en ambos estudios [⁶⁸Ga]Ga-DOTA-SSA/[¹⁸F]FDG, si Ki67<20% (G1 y G2) y en una minoría de pacientes con G3 Ki67>20%.
- PRRT como primera línea de tratamiento en NET no resecable o diseminada en una minoría de pacientes seleccionados con alta expresión de SSTR (basado en el riesgo y síntomas y ubicación del tumor primario).

Montserrat Negre
Medicina Nuclear
Hospital Universitari de Girona Dr. Josep Trueta

- Consideración de PRRT para retratamiento en pacientes con enfermedad estable o en remisión durante al menos un año después del final de la primera PRRT.
- PRRT en combinación con CAPTEM si Ki67>20% sólo en ensayos clínicos.
- [68Ga] Ga-DOTA-SSA PET/CT, en asociación con TC diagnóstico para el diagnóstico, incluida la detección de tumor primario desconocido, para la estadificación, para el re-estadiaje después de la cirugía, en caso de sospecha o diagnóstico de progresión y para la selección de la PRRT.
- [18F] FDG en TNE G3, en CNE, en aquellos casos con lesiones morfológicas en el TC sin captación de [68Ga]Ga-DOTA-SSA y en los casos que presenten rápida progresión independientemente del grado tumoral.
- [68Ga] Ga-DOTA-SSA en PPGL cuando se sospeche localización extra suprarrenal, con o sin lesiones por TC.



TGF- β 1 increases cellular invasion of colorectal neuroendocrine carcinoma cell line through partial epithelial-mesenchymal transition

Norihiko Sasaki^{a,1}, Seiichi Shinji^{b,c,*1}, Yuuki Shichi^c, Toshiyuki Ishiwata^c, Tomio Arai^d, Takeshi Yamada^b, Goro Takahashi^b, Ryo Ohta^b, Hiromichi Sonoda^b, Akihisa Matsuda^b, Takuma Iwai^b, Kohki Takeda^b, Kazuhide Yonaga^b, Koji Ueda^b, Sho Kuriyama^b, Toshimitsu Miyasaka^b, Hiroshi Yoshida^b

^a Research Team for Geriatric Medicine (Vascular Medicine), Tokyo Metropolitan Institute of Gerontology, Tokyo, 173-0015, Japan

^b Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, Tokyo, 113-8603, Japan

^c Division of Aging and Carcinogenesis, Research Team for Geriatric Pathology, Tokyo Metropolitan Institute of Gerontology, Tokyo, 173-0015, Japan

^d Department of Pathology, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, 173-0015, Japan

ARTICLE INFO

Keywords:

Neuroendocrine carcinoma
EMT
TGF- β 1
 α 2-integrin
Adhesion
Invasion

ABSTRACT

Epithelial-mesenchymal transition (EMT) plays a pivotal role in cancer progression and metastasis in many types of malignancies, including colorectal cancer. Although the importance of EMT is also considered in colorectal neuroendocrine carcinoma (NEC), its regulatory mechanisms have not been elucidated. We recently established a human colorectal NEC cell line, SS-2. In this study, we aimed to clarify whether these cells were sensitive to transforming growth factor beta 1 (TGF- β 1) and whether EMT could be induced through TGF- β 1/Smad signaling, with the corresponding NEC cell-specific changes in invasiveness. In SS-2 cells, activation of TGF- β 1 signaling, as indicated by phosphorylation of Smad2/3, was dose-dependent, demonstrating that SS-2 cells were responsive to TGF- β 1. Analysis of EMT markers showed that mRNA levels changed with TGF- β 1 treatment and that E-cadherin, an EMT marker, was expressed in cell-cell junctions even after TGF- β 1 treatment. Invasion assays showed that TGF- β 1-treated SS-2 cells invaded more rapidly than non-treated cells, and these cells demonstrated increased metalloprotease activity and cell adhesion. Among integrins involved in cell-to-matrix adhesion, α 2-integrin was exclusively upregulated in TGF- β 1-treated SS-2 cells, but not in other colon cancer cell lines, and adhesion and invasion were inhibited by an anti- α 2-integrin blocking antibody. Our findings suggest that α 2-integrin may represent a novel therapeutic target for the metastasis of colorectal NEC cells.

1. Introduction

Neuroendocrine neoplasms (NENs) are rare tumors originating from neuroendocrine cells that are widely distributed in the human body [1, 2]. In 2017, an International Agency for Research on Cancer and World Health Organization experts consensus proposal defined three types of neuroendocrine tumors, two types of neuroendocrine carcinoma (NEC), and mixed neuroendocrine-non-neuroendocrine neoplasm [3]. According to the epidemiological database established by the Surveillance,

Epidemiology, and End Results study in the United States, the incidence of NEN increased 6.4 times between 1973 and 2012, as did the number of locally localized cases [4]. Clinically, NEC is the most aggressive type of malignancy among NENs. NEC shows not only high proliferative capacities with a median Ki-67 labeling index of 80%, but also high metastatic capacity [5]. Novel therapeutic options are urgently required for patients with NEC because of NEC's resistance to chemotherapy and the increasing global incidence [6].

Epithelial-to-mesenchymal transition (EMT) is involved in cancer

Abbreviations: BSA, bovine serum albumin; CSC, cancer stem cell; EMT, epithelial-to-mesenchymal transition; FACS, fluorescence activated cell sorter; MFI, mean fluorescence intensity; MMP, matrix metalloproteinase; NEC, neuroendocrine carcinoma; NENs, neuroendocrine neoplasms; qRT-PCR, quantitative reverse transcription-polymerase chain reaction; SD, standard deviation; SEM, scanning electron microscopic; TGF, transforming growth factor-beta.

* Corresponding author. Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo, 113-8603, Japan.

E-mail address: s-shinji@nms.ac.jp (S. Shinji).

¹ These authors contributed equally to this study.

<https://doi.org/10.1016/j.bbrep.2022.101239>

Received 6 October 2021; Received in revised form 20 December 2021; Accepted 24 February 2022

Available online 1 March 2022

2405-5808/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Greissy Vázquez
Anatomía Patológica
Hospital Universitario Puerta de Hierro

TGF- β 1 increases cellular invasion of colorectal neuroendocrine carcinoma cell line through partial epithelial-mesenchymal transition

[**https://doi.org/10.1016/j.bbrep.2022.101239**](https://doi.org/10.1016/j.bbrep.2022.101239)

Comentario:

Clínicamente el carcinoma neuroendocrino es el tipo más agresivo de malignidad entre las neoplasias neuroendocrinas, tienen una alta capacidad proliferativa y metastásica con resistencia a la quimioterapia. La transición epitelio-mesénquima (EMT) juega un papel fundamental en la progresión del cáncer en muchos tipos de neoplasias malignas, incluido el cáncer colorrectal. Aunque la importancia de la EMT también se considera en carcinoma neuroendocrino colorrectal (NEC), sus mecanismos reguladores no han sido identificados.

En este estudio se realizó una línea celular de NEC colorrectal humano (SS-2), para saber si estas células eran sensibles a factor de crecimiento transformante beta 1 (TGF- β 1) y si la EMT podría inducirse a través de la señalización de TGF- β 1/Smad.

En las células SS-2, la activación de la señalización de TGF- β 1, como indicado por la fosforilación de Smad2/3, dependía de la dosis, lo que demuestra que las células SS-2 respondían a TGF- β 1.

El análisis de los marcadores de EMT mostró que los niveles de ARNm cambiaron con el tratamiento con TGF- β 1 y que la E-cadherina, un marcador EMT, se expresó en uniones célula-célula incluso después del tratamiento con TGF- β 1.

Los ensayos de invasión mostraron que las células SS-2 tratadas con TGF- β 1 invadieron más rápidamente que las células no tratadas, y estas células demostraron un aumento actividad metaloproteinasa y adhesión celular.

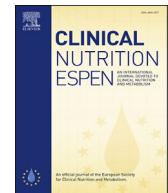
Entre las integrinas involucradas en la adhesión de célula a matriz, la integrina α 2 se reguló exclusivamente en células SS-2 tratadas con TGF- β 1, pero no en otras líneas celulares de cáncer de colon, la adhesión y la invasión fueron inhibidas por un anticuerpo bloqueador de la integrina anti- α 2.

Los hallazgos de este estudio sugieren que la integrina α 2 puede representar un nuevo objetivo terapéutico para la metástasis de las células NEC colorrectales.



ELSEVIER

Contents lists available at ScienceDirect

Clinical Nutrition ESPENjournal homepage: <http://www.clinicalnutritionespen.com>

Original article

Exploring health professional knowledge and management of nutritional complications in neuroendocrine cancer patients: Results of an international multidisciplinary surveyErin Laing ^{a, b, *}, Nicole Kiss ^{c, d}, Meinir Krishnasamy ^{a, e, f}, Karla Gough ^g, Michael Michael ^h^a Department of Nursing, School of Health Sciences, The University of Melbourne, 305 Grattan Street, Melbourne, VIC, 3000, Australia^b Nutrition and Speech Pathology Department, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia^c Institute for Physical Activity and Nutrition (IPAN), Deakin University, 221 Burwood Highway, Burwood, VIC, 3125, Australia^d Allied Health Research, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia^e Victorian Comprehensive Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia^f Academic Nursing Unit, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia^g Department of Health Services Research, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia^h Neuroendocrine Unit (ENETs COE), Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia**ARTICLE INFO****Article history:**

Received 20 December 2021

Accepted 28 February 2022

Keywords:

Neuroendocrine

Malnutrition

Nutrition

Screening

Survey

SUMMARY

Background and aims: Patients with neuroendocrine tumours (NET) are at nutritional risk due to symptoms and treatment side-effects. Current evidence-based guidelines lack information regarding optimal nutritional management. This study aimed to describe health professional knowledge and management of nutrition complications in GEP NET patients and summarise current international practice.

Methods: Multidisciplinary health professionals who regularly provide care for NET patients, were invited to participate in a 21-item online survey. Survey questions asked about symptom prevalence, nutrition screening, assessment practices, and vitamin deficiency screening and supplementation practices. General demographic information was recorded.

Results: In total 73 health professionals completed the survey. Many worked in Australia (52%) and the United Kingdom (19%). Most responses were provided by medical oncologists (25%), nurses (23%) and dietitians (30%). Diarrhoea and fatigue were reported as the most common symptoms (86% and 60%, respectively) and of greatest concern to patients with NET (80% and 52%, respectively). Provision of advice for symptom management, weight loss and food intolerances was reported by 92%, 59% and 41%, respectively. Overall, 38% carried out screening/assessment for malnutrition and screening for vitamin deficiencies, respectively. Health professionals reported on the lack of NET-specific nutrition guidelines and hence used general oncology nutrition guidelines to direct their practice.

Conclusions: This is the first international survey of nutrition knowledge and practices among NET health professionals. Results highlight variations in nutrition screening and assessment practices and identify a gap in NET-specific guidelines addressing nutrition issues in this at-risk patient group.

© 2022 European Society for Clinical Nutrition and Metabolism. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Neuroendocrine tumours (NET) are a heterogeneous, often indolent group of cancers, with varying prognoses. They are commonly located in the gastrointestinal (GI) tract, pancreas and lung, and have the unique potential to secrete hormones resulting

* Corresponding author. Nutrition and Speech Pathology Department, Peter MacCallum Cancer Centre, Victorian Comprehensive Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia.

E-mail address: Erin.Laing@petermac.org (E. Laing).

Miguel Antonio Sampedro-Núñez
Endocrinología
Hospital Universitario de La Princesa

**Exploring health professional knowledge and management of nutritional complications in neuroendocrine cancer patients:
Results of an international multidisciplinary survey**

<https://doi.org/10.1016/j.clnesp.2022.02.124>

Comentario:

Los tumores neuroendocrinos son el paradigma de una enfermedad heterogénea en la cual se van a mezclar una serie de factores dependientes del tumor (si este es un tumor funcionante o no), tratamientos que pueden ser muy diversos (cirugía, quimioterapia, radioterapia, el uso de análogos, everolimus o sunitinib), a lo cual también se van a sumar factores del paciente (sus enfermedades previas o también el deterioro físico y psicológico que puede estar asociado). Todos estos serán factores que condicionarán un ambiente de inflamación sistémica, alteraciones metabólicas y alteraciones digestivas que son el sustrato necesario para el desarrollo de una desnutrición relacionada con enfermedad. Las guías actuales carecen de información sobre el manejo nutricional de estos pacientes. Este reciente estudio tuvo como objetivo describir el conocimiento de los profesionales de la salud y el manejo de las complicaciones nutricionales en pacientes con tumores neuroendocrinos gastroenteropancreáticos y busca resumir la práctica actual con una encuesta de 21 preguntas.

En total 73 profesionales de la salud completaron la encuesta [principalmente de Australia (52 %) y el Reino Unido (19 %)]. La mayoría de las respuestas fueron proporcionadas por médicos oncólogos (25 %), enfermeras (23 %) y dietistas (30 %). La diarrea y la fatiga se informaron como los síntomas más comunes (86 % y 60 %, respectivamente). No obstante, solo el 38 % de los expertos realizaba pruebas de detección/evaluación de desnutrición y pruebas de detección de deficiencias vitamínicas, respectivamente. Los profesionales de la salud informaron sobre la falta de pautas nutricionales específicas para tumores neuroendocrinos y, por lo tanto, utilizaron pautas generales de nutrición oncológica para dirigir su práctica.

Conclusiones:

Ésta es la primera encuesta internacional sobre conocimientos y prácticas de nutrición entre profesionales de la salud especializados en tumores neuroendocrinos. Estamos en la necesidad de guías específicas para este grupo de pacientes.

Lavinia Benini
Oncology Department
Azienda Ospedaliera Universitaria Integrata Verona, Italy.

CASO CLÍNICO

We present the case of a 59 y.o. woman, with past history of hypertension, dyslipidemia and kidney chronic failure (due to nephrectomy).

- In June 2013, for urinary infection, she performed investigations leading to the finding of a left kidney mass, which initially just underwent follow-up.
- In February 2015 eventually was performed a left nephrectomy, with the pathological report of: Neuroendocrine Cancer, pT3a, ki67 35%. It was asked a pathological revision at the Memorial Sloan Kettering Cancer Center (New York), confirming the previous diagnosis.
- The patient then started Somatostatin LAR 20mg/28d, as adjuvant treatment.
- April 2016: hepatic and bone relapse.
- Was then started a first line chemotherapy with Carboplatin-Etoposide, for 5 cycles. Best response was Partial Response on the liver metastasis and Stable disease on the bone.
- October 2016: hepatic, peritoneal and bone PD.
- II line with Everolimus and Sandostatin LAR 40 mg/28 mg.
- May 2018: hepatic and bone PD; palliative RT was performed on symptomatic lumbar lesions.
- July 2018: III line treatment with Capecitabine-Temozolomide. BOR: SD
- 06/02/2019 The patient came as second opinion at the Oncology Department of Vall d'Hebron Hospital; were hence requested functional and anatomical investigations.
- 22/02/2019 CT scan: multiple liver metastasis (mayor lesion in S8 of 38 mm); stable multiple osteosclerotic lesion, stable multiple retroperitoneal nodes.
- FDG-PET: just hypermetabolic areas at right iliac wing and ischium; no contrast uptake of the other known lesions.
- Gallium-PET: multiple hepatic lesions (the bigger in S8 of 29x45mm, SUV max 59), conglomerate node metastasis peri-pancreatic (SUV max 121) and at the minor gastric curve (SUV max 67), common iliac lymph nodes (SUV max 16); diffuse bone lesions with high uptake.
- Considering the extension of the disease, the progression under many lines of the chemo and the different behavior at functional imaging (FDG negative, Gallium-positive), it was decided to stop the chemo. The patient started Somatostatin 120 mg/28d, with initial PR.
- December 2019: bone and hepatic PD
- 19/12/2019 The case was discussed with the Multidisciplinary team, and it was decided to go for PRRT.
- 30/01/2020: 1° cycle of PRRT, 5° therapeutic line.

Lavinia Benini
Oncology Department
Azienda Ospedaliera Universitaria Integrata Verona, Italy.

CASO CLÍNICO

- May 2020: CT scan performed after 3 cycles of PRRT showed new lung micronodules at the right inferior lobe; hepatic and bone SD. The case was discussed at multidisciplinary meeting, and despite the suspected lung progression, it was decided to keep on PRRT.
- 14/07/2020 4° and last cycle of PRRT.
- 27/11/2020 Gallium-PET: CR of lung nodules and cervical nodes. PR of the liver (75x48mm > 21x31mm, SUV max 33), pancreas, retroperitoneal nodes (SUV max 98> 22), bone (SUV max 45>13) and pelvic lesion (SUV max 88>25).
- 27/01/2021 Gallium-PET: further metabolic response of retroperitoneal nodes (SUV max 19 > 10), pelvic mass (SUV max 25 > 23), liver. Uptake stability of the pancreas and the bone.
- 30/04/2021 CT scan: liver PR (greater lesion 52 > 24 mm); SD of bone and lung lesions.
- The great response to PRRT was maintained until January 2022.
- 14/01/2022 CT scan: hepatic progression with multiple confluent lesions; 23mm-lesion of the pancreatic body. SD of the bone.
- 20/01/2022 liver biopsy. The histologic report proved a well-differentiated neuroendocrine tumor, ki67 20%, 7 mitotic index/10 HPF; CDX2 -, TTF1 -. The NGS panel reported no targetable-mutations, just VUSs with no evidence of renal or NET neoplasia reported in the literature; TMB 6.72 mutations/megabase.
- 10/02/2022 Multidisciplinary discussion: patient candidate to PRRT-rechallenge.

Discussion

Neuroendocrine neoplasms (NENs) are heterogeneous malignant diseases arising in the 85% of the cases within the gastrointestinal system or the lungs (1); nevertheless, they can potentially develop in any organ system. The genitourinary system is rarely involved by NENs, and primary NENs of the genitourinary tract represent less than 1-2% of all the GU malignancies (2); they are most frequently arising from the prostate, even though the involvement of the kidneys (as well as urinary bladder, testes, ovaries, and the uterus) is possible.

Neuroendocrine cells can be found in the renal pelvis, but not in the renal parenchyma: an origin from intrinsic NE cells of the normal urinary tract is hence less likely, and the most accepted histogenesis hypothesis is that renal NETs differentiate from neuroendocrine-committed, primitive totipotential cell lines.

According to the last WHO Classification of Tumors of the Urinary System and Male Genital Organs (3) NENs are subclassified into well-differentiated neuroendocrine tumors (NET; previously called "carcinoids"), large cell neuroendocrine carcinoma (LC-NEC), small cell neuroendocrine carcinoma (SC-NEC), and pheochromocytoma.

Lavinia Benini
Oncology Department
Azienda Ospedaliera Universitaria Integrata Verona, Italy.

CASO CLÍNICO

The renal-NETs usually have a more indolent evolution, whereas the prognosis of NEC is poor (75% of patients die from their disease within a year (4, 5). The tumor usually presents when has reached large dimensions and already invading into perirenal adipose tissue, with nodal involvement. Eventually, distant metastases occur in brain, bone, adrenal gland, and liver.

There is still few literature on renal NETS, mainly single center-reports (6, 7); the largest series presented was in the French group (8), considering 27 patients with sporadic G 1-2 renal NETs; it confirmed tumor size and presence of metastasis as the most important prognostic factors.

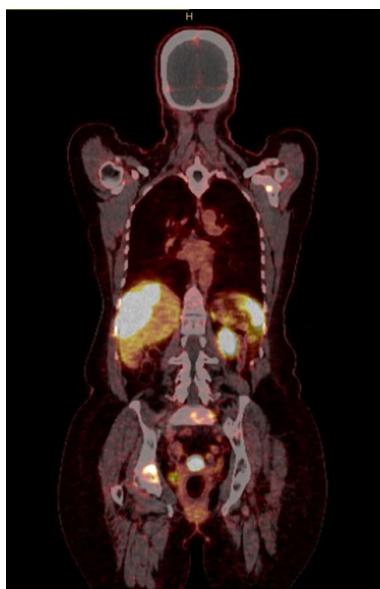
The rarity of these tumors, as long of the frequently-severe prognosis, carries several concepts to keep in mind when dealing with NENs of the GU tract: firstly, it is necessary to look for differential diagnostic hypothesis and search for primaries outside the GU tract before rendering to such diagnosis; the presence of Neuroendocrine markers is necessary to rule out other primary renal tumors. Secondly, there is no consensus for treatment guidelines, and the regimens used are derived from the treatment of NENs from Gastrointestinal district; the surgery on primary tumor is the only curative treatment, whereas SSA and poli-chemotherapy regimens are the preferred medical strategies.

The histology of the case presented above has been reviewed by an excellence Center (MSKCC), and the second biopsy performed in January 2022 also confirmed the previous diagnosis, so it is really trustworthy.

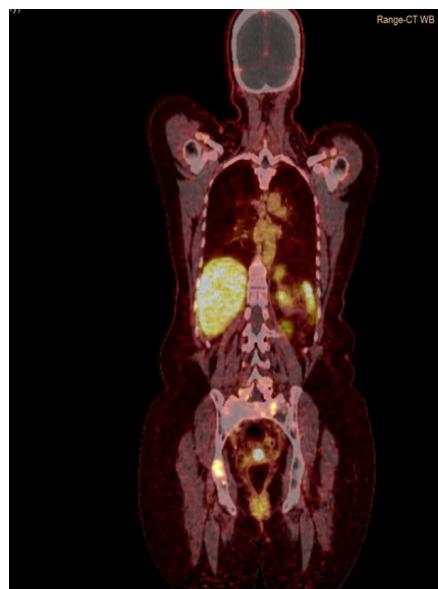
The case is quite interesting for the discrepancy between the histo-cytologic report and the clinical outcome: it's been almost 12 years since the first detection of the renal mass (as previously said, the prognosis for high grade renal NET is far poorer).

This case also shows an urgent unmet need for renal-NET, which is the availability of a biomarker to predict those patients that could benefit the most from our treatment; it is still lacking a deep knowledge in a specific pathway involved in the pathogenesis of these tumors. According to the literature (10), the mutational profile is variable, the most frequently mutated genes being TET2 and CDH1. However, in our case no relevant mutation has been found in the NGS panel.

January 2020

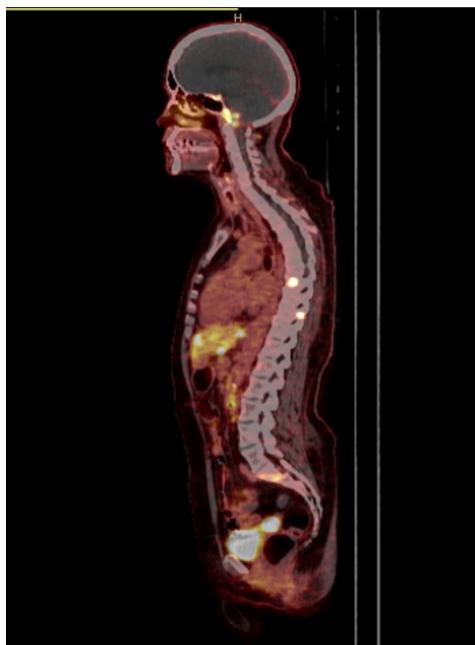
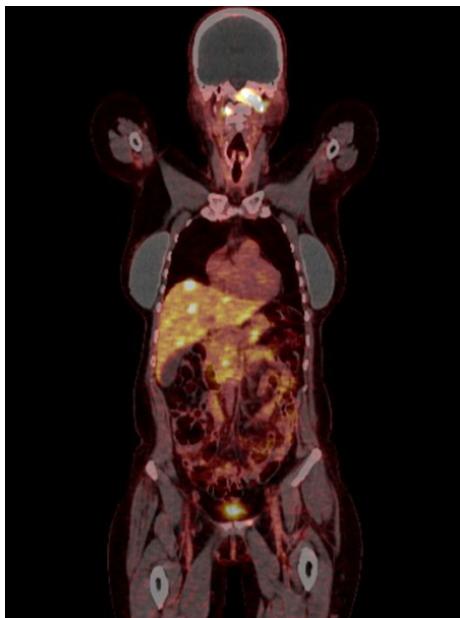


November 2020



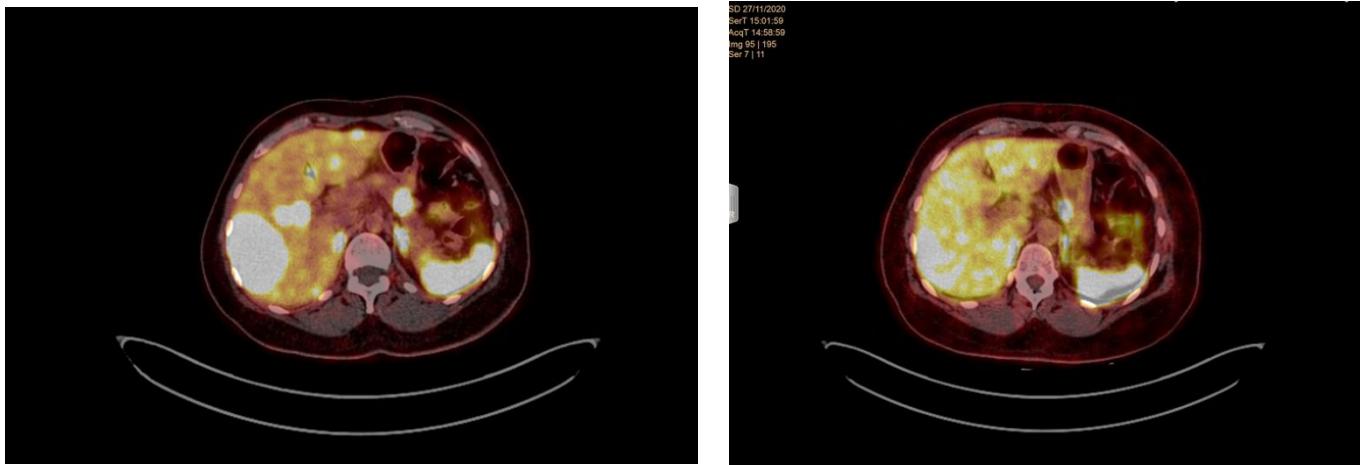
Lavinia Benini
Oncology Department
Azienda Ospedaliera Universitaria Integrata Verona, Italy.

CASO CLÍNICO



Lavinia Benini
Oncology Department
Azienda Ospedaliera Universitaria Integrata Verona, Italy.

CASO CLÍNICO



Bibliography

- 1) Taal B, G, Visser O: Epidemiology of Neuroendocrine Tumours. *Neuroendocrinology* 2004;80(suppl 1):3-7. doi: 10.1159/000080731
- 2) Strosberg JR, Coppola D, Klimstra DS, Phan AT, Kulke MH, Wiseman GA, Kvols LK: The NANETS Consensus Guidelines for the Diagnosis and Management of Poorly Differentiated (High-Grade) Extrapulmonary Neuroendocrine Carcinomas. *Pancreas* 39(6): 799-800, 2010.
- 3) Holger Moch, Antonio L. Cubilla, Peter A. Humphrey, Victor E. Reuter, Thomas M. Ulbright, The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and testicular Tumours, *European Urology*, Volume 70, Issue 1, 2016, Pages 93-105, ISSN 0302-2838, <https://doi.org/10.1016/j.eururo.2016.02.029>.
- 4) Essenfeld H, Manivel JC, Benedetto P, Albores-Saavedra J. Small cell carcinoma of the renal pelvis: a clinicopathological, morphological and immunohistochemical study of 2 cases. *J Urol* 1990; **144**: 344-7
- 5) R. Mazzucchelli, D. Morichetti, A. Lopez-Beltran, et al. **Neuroendocrine tumours of the urinary system and male genital organs: clinical significance** *BJU Int*, 103 (11) (2009), pp. 1464-1470, 10.1111/j.1464-410X.2009.08451.x
- 6) Teegavarapu P.S., Rao P., Matrana M., Cauley D.H., Wood C.G., Tannir N.M. Neuroendocrine tumors of the kidney: A single institution experience (2014) *Clinical Genitourinary Cancer*, 12 (6), pp. 422 – 427 DOI: 10.1016/j.clgc.2014.06.008 [LB1]
- 7) McGarrah PW, Westin GFM, Hobday TJ, Scales JA, Ingimarsson JP, Leibovich BC, Halldanarson TR. Renal Neuroendocrine Neoplasms: A Single-center Experience. *Clin Genitourin Cancer*. 2020 Aug;18(4):e343-e349. doi: 10.1016/j.clgc.2019.11.003. Epub 2019 Dec 5. PMID: 31911122.
- 8) Chevalier B, Tilmant A, Espiard S, Hentic O, Niccoli P, Pracht M, Lecomte T, Perrier M, Drui D, Baudin E, Aubert S, Do Cao C. Clinical and pathological characterization of renal Neuroendocrine Tumor (rNET): A national retrospective study from the French Group of Endocrine Tumors (GTE) Abstract #3139. 18th Annual ENETS Conference 2021 (2021)
- 9) Ahmed N. Shehabeldin, Jae Y. Ro, Neuroendocrine tumors of genitourinary tract: Recent advances, *Annals of Diagnostic Pathology*, Volume 42, 2019, Pages 48-58, ISSN 1092-9134, <https://doi.org/10.1016/j.anndiagpath.2019.06.009>.
- 10) Pivovarcikova, K, Agaimy, A, Martinek, P, Alaghehbandan, R, Perez-Montiel, D, Alvarado-Cabrero, I, Rogala, J, Kuroda, N, Rychly, B, Gasparov, S, Michalova, K, Michal, M, Hora, M, Pitra, T, Tuckova, I, Laciok, S, Mareckova, J & Hes, O, Primary renal well-differentiated neuroendocrine tumour (carcinosoid): next-generation sequencing study of 11 cases. (2019) *Histopathology* 75, 104– 118. <https://doi.org/10.1111/his.13856>

Secretaría Técnica GETNE

MFAR Barcelona
Balmes 243, Escalera A 5º1^a
08006 Barcelona
Teléfono: +34 93 434 44 12

Persona de contacto:
María Montero 690 127 772

getne.academy@getne.org
getne@getne.org



www.getne.org

