BiblioGETNE

Nº3 - Septiembre 2021

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GETNE ACADEMY
Introducción
Artículos y comentarios de cada especialidad

GETNE
Grupo Español de Tumores Neuroendocrinos y Endocrinos

GETNE ACADEMY

- Grupo multidisciplinar dentro del Grupo GETNE que cuenta con el apoyo de su Junta Directiva y que está tutelado directamente por el Dr. Jaume Capdevila (Presidente GETNE), Dr. Jorge Barriuso y Dra. Maribel del Olmo (vocales GETNE).

- Abierto a todos los socios.

- Compuesto inicialmente por los siguientes representantes y especialidades de cada una: Cirugía General (Dr. José Luis Muñoz de Nova), Endocrinología (Dr. Miguel Sampedro), Medicina Nuclear (Dra. Eva María Triviño), Anatomía Patológica (Dra. Greissy Vázquez), Oncología Médica (Dr. Jorge Hernando).

- **Objetivos:**
  1. Creación de una red de profesionales jóvenes interesados en el diagnóstico, tratamiento e investigación de los tumores endocrinos y neuroendocrinos.
  2. Revisión y potenciación de ideas de proyectos de investigación.
  3. Elaboración de propuestas educacionales.
  4. Apoyo a iniciativas que pueda ayudar al desarrollo de las nuevas generaciones.

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Introducción

GETNE ACADEMY tiene el placer de enviar el tercer 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.

Esperamos que sea de vuestro interés.

Un cordial saludo,
GETNE ACADEMY

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Original Research

Coronavirus disease 2019 in patients with neuroendocrine neoplasms: Preliminary results of the INTENSIVE study

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KEYWORDS
Neuroendocrine

Abstract ***Background:*** Specific data regarding coronavirus disease 2019 (COVID-19) in patients with neuroendocrine neoplasms (NENs) are lacking. The aim of this study is to describe

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Coronavirus disease 2019 in patients with neuroendocrine neoplasms: Preliminary results of the INTENSIVE study

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Comentario:

En los últimos meses se han publicado diferentes estudios que revisan el impacto del COVID19 en los pacientes oncológicos. Con respecto a los tumores neuroendocrinos, destacamos el presente artículo que recoge los datos de pacientes entre junio de 2020 y marzo 2021.

Se incluyeron 89 pacientes en 8 centros internacionales, que habían tenido una PCR de COVID19 positiva con un tumor neuroendocrino activo (excepto carcinoma microcítico de pulmón). La mortalidad de la cohorte fue del 7.8%, aunque la mayoría de los pacientes no tuvieron que realizar cambios en sus planes terapéuticos y se recuperaron de la infección sin secuelas.

La conclusión principal del estudio es que el impacto de la pandemia COVID19 en los pacientes con tumores neuroendocrinos es similar al de la población general, con una elevada tasa de recuperación sin secuelas ni cambios en el plan terapéutico.

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ORIGINAL ARTICLE

Evaluation of circulating transcript analysis (NETest) in small intestinal neuroendocrine neoplasms after surgical resection

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Abstract

Purpose Surgical resection is the only effective curative strategy for small intestinal neuroendocrine neoplasms (SINENs). Nevertheless, the evaluation of residual disease and prediction of disease recurrence/progression remains a problematic issue.

Methods We evaluated 13 SINENs that underwent surgical resection of the primary tumour and/or mesenteric mass. Patients were divided in three groups: (a) Group 1: SINENs that underwent resection with curative intent, (b) Group 2: SINENs treated with resection in the setting of metastatic disease, which remained stable and (c) Group 3: SINENs treated with resection in the setting of metastatic disease, with evidence of any progression at follow-up. NETest and chromogranin A were measured pre-operatively and post-operatively during a 22-month median follow-up period and compared with imaging studies. NETest score <20% was determined as normal, 20–40% low, 41–79% intermediate and ≥80% high score.

Results NETest score was raised in all (100%) SINENs pre-operatively. Surgery with curative intent resulted in NETest score reduction from 78.25 ± 15.32 to 25.25 ± 1.75 ($p < 0.05$). Low NETest scores post-operatively were evident in all cases without clinical evidence of residual disease (Group 1). However, the low disease activity score suggested the presence of microscopic residual disease. In three cases (75%) with stable disease (Group 2) the NETest score was low consistent with indolent disease. In the progressive disease group (Group 3), a high NETest score was present in three cases (60%) and an intermediate NETest score in the remainder (40%).

Conclusions Blood NETest scores accurately identified SINENs and were significantly decreased by curative surgery. Monitoring NETest post-operatively may facilitate management by identifying the presence of residual/progressive disease.

Keywords Neuroendocrine tumour · Small bowel · Surgery · NETest

These authors contributed equally: Faidon-Marios Laskaratos, Man Liu

Supplementary information The online version of this article (https://doi.org/10.1007/s12020-020-02289-2) contains supplementary material, which is available to authorized users.

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Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of malignancies that arise from neuroendocrine cells of the diffuse neuroendocrine system. The most common disease sites are the gastrointestinal tract, pancreas and the bronchopulmonary system [1]. Small intestinal neuroendocrine neoplasms (SINENs) arise in the jejunum and ileum and represent 26% of all diagnosed NENs [2–4]. SINENs often present late with extensive liver and nodal metastases due to the nonspecific nature of their symptomatology and lack of clinical recognition [2]. Nevertheless, resection of the primary tumour and mesenteric mass is usually advocated, since retrospective studies have noted that resection confers survival advantage by preventing local complications and controlling systemic symptoms. It should be noted, however, that these analyses are limited by selection

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Evaluation of circulating transcript analysis (NETest) in small intestinal neuroendocrine neoplasms after surgical resection

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Comentario:

Numerosos artículos están analizando el papel de los miRNA en los TNE en los últimos años. Los principales aspectos estudiados son la capacidad de detectar enfermedad residual tras una resección quirúrgica y el posible papel pronóstico de sus niveles.

En este trabajo se evalúa la correlación de las puntuaciones del NETest y la CgA con la presencia de enfermedad tumoral y su comportamiento. Se incluyeron 13 pacientes seguidos de forma prospectiva que fueron sometidos a una resección quirúrgica por un TNE intestinal. Cuatro pacientes fueron intervenidos con finalidad curativa, 4 en el contexto de metástasis que permanecieron estables y 5 con enfermedad que progresó durante el seguimiento (seguimiento mediano: 22 meses).

El NETest se encontraba elevado en todos los pacientes de forma preoperatoria y disminuyó de forma significativa en los pacientes curados, pero no en los otros dos grupos. La CgA estaba elevada en el 60% y no se modificó significativamente tras la cirugía. A su vez, el NETest mostró valores significativamente mayores en los pacientes en los que la enfermedad progresó durante el seguimiento frente a aquellos en los que permaneció estable (área bajo la curva de 0,844; sensibilidad 100% y especificidad 78%).

Los datos de este y otros trabajos similares sugieren que la famosa heterogeneidad de los TNE podría ser caracterizada al menos en parte por los miRNA, que jugarían un papel relevante a la hora de la detectar enfermedad subclínica y determinar el comportamiento de la enfermedad. Estudios de mayor potencia deben validar estos datos.

Clinical Assessment of ^{177}Lu-DOTATATE Quantification by Comparison of SUV-Based Parameters Measured on Both Post-PRRT SPECT/CT and ^{68}Ga-DOTATOC PET/CT in Patients With Neuroendocrine Tumors

A Feasibility Study

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Introduction: The aim of this study was to study the feasibility of an SUV-based ^{177}Lu-DOTATATE SPECT/CT quantification and to assess the correlation of different parameters with the corresponding measured on ^{68}Ga-DOTATOC PET/CT in patients with well-differentiated gastroenteropancreatic neuroendocrine tumors (WD-GEP-NET) treated with peptide receptor radionuclide therapy.

Patients and Methods: Patients with WD-GEP-NET who benefited from a pretherapeutic ^{68}Ga-DOTATOC PET/CT and a ^{177}Lu-DOTATATE SPECT/CT after the cycle 1 of peptide receptor radionuclide therapy were prospectively included. SPECT/CT acquisitions were performed on a system calibrated with a conversion factor of 9.48 counts/MBq per second and were reconstructed with an iterative algorithm allowing quantification using the SPECTRA Quant software (MIM Software, Cleveland, OH). For each patient, different SUV parameters were recorded on both PET/CT (Ga parameters) and SPECT/CT (Lu parameters) for comparison: physiological uptakes (liver/spleen), tumor uptake (1–10/patient; SUV_{max}, SUV_{mean}, SUV_{peak}, MTV), tumor-to-liver and tumor-to-spleen ratios according to liver/spleen SUV_{max} and SUV_{mean} (TLR_{max}, TLR_{mean}, TSR_{max}, and TSR_{mean}, respectively).

Results: Ten patients (8 female; 2 male) aged from 50 to 83 years presenting with a metastatic progressive WD-GEP-NET (7 small intestine, 2 pancreas, 1 rectum) were included. Median values of lesional Lu-SUV were significantly lower than the corresponding Ga-SUV ($P < 0.001$), whereas median values of lesional Lu-MTV, Lu-TLR, and Lu-TSR were significantly higher than the corresponding Ga-MTV, Ga-TLR, and Ga-TSR ($P < 0.02$). Pearson correlation coefficients were strong for both SUV and MTV parameters (0.779–0.845), weak for TLR parameters (0.365–0.394), and moderate-to-strong for TSR parameters (0.676–0.750).

Conclusions: Our results suggest the feasibility of ^{177}Lu-DOTATATE SPECT/CT quantification in clinical practice and show a strong correlation of several SUV-based parameters with the corresponding in ^{68}Ga-DOTATOC PET/CT.

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Key Words: SPECT/CT quantification, ^{68}Ga-DOTATOC PET/CT, neuroendocrine tumor, ^{177}Lu-DOTATATE peptide receptor radionuclide therapy

(*Clin Nucl Med* 2021;46: 111–118)

Management of patients with metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors (WD-GEP-NET) who progressed after a first-line treatment with somatostatin analogs (SSAs) has remained controversial for many years, until novel therapeutic options have recently become available (regional therapy in case of metastatic liver disease [ie, transarterial chemoembolization, radiofrequency ablation], targeted therapy, chemotherapy).[1] The recent advent of ^{177}Lu-DOTATATE peptide receptor radionuclide therapy (PRRT) in the management of midgut NETs[2] has greatly changed the recommendations. Indeed, following the results of a phase 3 randomized NETTER trial, a marketing authorization has been granted for its use in second-line of inoperable or metastatic WD-GEP-NETs progressive under SSA, and expressing somatostatin receptors (SSTRs).

The response to PRRT depends mainly on the expression of SSTRs on target lesions. Recent studies have shown that the semi-quantitative parameters based on SUV in pretherapeutic ^{68}Ga-DOTApeptides PET/CT may be correlated with the therapeutic response after PRRT.[3,4] However, the SUV_{max} threshold allowing to predict therapeutic response varies among studies (ranging from 10.2 to 16.4) with improvable performances (sensibility of 83%–95% and specificity of 60%–84%).[3,4] Moreover, changes in SUV parameters (delta-SUV from baseline to end of PRRT) were not necessarily correlated with the therapeutic response.[5,6] Thus, there is a need to improve the quantification in imaging for the pretherapeutic assessment and follow-up evaluation of patients treated with ^{177}Lu-DOTATATE PRRT.

According to the protocol proposed in the NETTER study, the current prescription for PRRT consists of 4 cycles of ^{177}Lu-DOTATATE with a planned dose of 7.4 GBq per cycle.[2] Sandström et al[7] hypothesized that ^{177}Lu-DOTATATE posttherapy 3D SPECT could be used to determine the maximum number of treatment cycles administered to the patient while remaining within the dose limits absorbed per organ. Thus, the development of a validated SUV-based approach in SPECT imaging would be interesting to better understand the distribution of ^{177}Lu-DOTATATE after the first PRRT cycle and then to propose a personalized regimen. Regarding patient's outcome, the first studies assessing the prognostic

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Clinical Assessment of ^{177}Lu-DOTATATE Quantification by Comparison of SUV-Based Parameters Measured on Both Post-PRRT SPECT/CT and ^{68}Ga-DOTATOC PET/CT in Patients With Neuroendocrine Tumors

https://doi.org/10.1097/rlu.0000000000003412

Comentario:

La publicación de los resultados del estudio NETTER-1 permitió la inclusión del tratamiento con ^{177}Lu-DOTATATE (PRRT) en las GPC como terapia de segunda línea de los TNE gastro-entero-pancreáticos bien diferenciados metastásicos e inoperables.

La respuesta a la PRRT depende principalmente de la expresión de receptores de la somatostatina en las lesiones diana. Aunque estudios recientes han demostrado que los parámetros semicuantitativos, basados en el cálculo del SUV, del estudio PET/TC con ^{68}Ga-DOTA-péptidos pueden estar correlacionados con la respuesta terapéutica, actualmente continúa siendo necesario un protocolo de cuantificación basado en las técnicas de imagen multimodalidad (SPECT/TC vs. PET/TC) para la evaluación de la respuesta a la PRRT.

La validación de un método de cuantificación en las imágenes SPECT/TC permitiría comprender mejor la distribución de ^{177}Lu-DOTATATE y proponer un régimen terapéutico personalizado. Dicho método, se basa en la definición de un factor de conversión que permita convertir el número de cuentas del estudio gammagráfico en unidades de concentración de la fuente de radiación (becquerelio/ml).

El presente estudio presenta los resultados de un protocolo de cuantificación, basado en el SUV, en el estudio SPECT/TC realizado a las 24 horas del primer ciclo ^{177} Lu-DOTATATE SPECT/TC. Incluyen un total de 10 pacientes en los que, además, evalúan la correlación de los diferentes parámetros semicuantitativos (SUV máximo, mínimo, medio, ratio tumor/hígado y ratio tumor/bazo) con los obtenidos en el estudio PET/TC con ^{68} Ga-DOTATOC realizado antes de iniciar la terapia con PRRT. Se trata del primer

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estudio que evalúa clínicamente la validez de la cuantificación del ^{177}Lu-DOTATATE SPECT/TC comparando los parámetros basados en el cálculo del SUV en la gammagrafía post-PRRT. Entre los resultados obtenidos, cabe destacar que respecto al ^{68}Ga-DOTATOC PET/TC, la mediana de los valores de SUV fueron significativamente menores en el estudio ^{177}Lu-DOTATATE SPECT/TC, mientras que la ratio tumor/hígado y tumor/bazo mostraron valores significativamente mayores. En cuanto la carga tumoral, medida mediante el cálculo del MTV (*metabolic tumor volumen*), encuentran que los valores de MTV fueron significativamente mayores en ^{177}Lu-DOTATATE SPECT/TC, especialmente para lesiones pequeñas. Los parámetros de SUV y MTV mostraron una correlación fuerte entre ambos estudios, siendo el SUVpico el único parámetro con un coeficiente de correlación >0.8 independientemente del MTV.

En base a sus resultados justifican la necesidad de estudios futuros con una cohorte más grande y un seguimiento a largo plazo para evaluar el valor de la cuantificación del 177Lu-DOTATATE SPECT/TC en la predicción de la respuesta terapéutica y la optimización de la dosimetría.

INSM1 is a Sensitive and Specific Marker of Neuroendocrine Differentiation in Head and Neck Tumors

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Abstract: The head and neck is the site of a wide and sometimes bewildering array of neuroendocrine (NE) tumors. Although recognition of NE differentiation may be necessary for appropriate tumor classification and treatment, traditional NE markers such as synaptophysin, chromogranin, and CD56 are not always sufficiently sensitive or specific to make this distinction. Insulinoma-associated protein 1 (INSM1) is a novel transcription factor that has recently demonstrated excellent sensitivity and specificity for NE differentiation in various anatomic sites, but has not yet been extensively evaluated in tumors of the head and neck. We performed INSM1 immunohistochemistry on NE tumors (n = 97) and non-NE tumors (n = 626) across all histologic grades and anatomic subsites of the head and neck. INSM1 was positive in all types of head and neck NE tumors evaluated here (99.0% sensitivity), including middle ear adenoma, pituitary adenoma, paraganglioma, medullary thyroid carcinoma, olfactory neuroblastoma, small cell carcinoma, large cell NE carcinoma, and sinonasal teratocarcinosarcoma. Notably, it was positive in the vast majority of high-grade NE malignancies (95.8% sensitivity). INSM1 also was negative in almost all non-NE tumors (97.6% specificity) with the highest rates of reactivity in alveolar rhabdomyosarcoma and SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1 (SMARCB1)-deficient sinonasal carcinoma. These findings confirm that INSM1 may be used as a standalone first-line marker of NE differentiation for tumors of the head and neck.

Key Words: head and neck tumors, neuroendocrine tumors, INSM1, immunohistochemistry, surgical pathology

(*Am J Surg Pathol* 2018;42:665–671)

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BACKGROUND

The head and neck is home to a broad and sometimes bewildering assortment of benign and malignant neuroendocrine (NE) tumors including middle ear adenoma, pituitary adenoma, paraganglioma, medullary thyroid carcinoma, olfactory neuroblastoma, small cell carcinoma, large cell NE carcinoma, and sinonasal teratocarcinosarcoma. In the pathologic diagnosis of head and neck tumors, the documentation of NE differentiation plays a vital role in appropriate tumor classification for prognostic and therapeutic purposes.[1–7] Despite the central role now played by immunohistochemistry as the primary means of identifying NE differentiation, the utility of the traditional NE markers synaptophysin, chromogranin, and CD56 can be limited. First, the individual and combined sensitivities of these markers is only 50% to 80% for high-grade NE tumors of the head and neck.[8–12] Second, traditional NE markers can also be expressed in a wide range of non-NE tumors, including carcinomas, sarcomas, and melanoma.[13–22] Third, the uncertain fidelity of cytoplasmic staining as an indicator of true NE differentiation can lead to equivocal results in cases with weak and/or focal reactivity. Because of these drawbacks, there is a need for a NE marker that is sensitive, specific, and exhibits nuclear expression that is biologically linked to the activation of NE differentiation.

Insulinoma-associated protein 1 (INSM1) is a transcription factor that has recently emerged as a useful diagnostic marker of NE differentiation. INSM1 expression has been tightly coupled to NE differentiation in normal and neoplastic tissues across a wide range of anatomic sites including the pancreas, gastrointestinal tract, lung, central nervous system, and peripheral nervous system.[23–29] In the head and neck specifically, INSM1 is known to play a role in the development of the olfactory neuroepithelium.[30] We have recently noted that, as a diagnostic adjunct to discern NE differentiation, INSM1 is particularly useful in the diagnosis of high-grade NE carcinomas of the thoracic cavity because it shows superior sensitivity and specificity compared with traditional NE markers synaptophysin, chromogranin, and CD56.[31] The role of INSM1 immunohistochemistry, however, has not been extensively evaluated for tumors of the head and neck.

METHODS

The surgical pathology archives at The Johns Hopkins Hospital were searched for all head and neck NE tumors diagnosed between January 1997 and December 2017. All

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INSM1 is a Sensitive and Specific Marker of Neuroendocrine Differentiation in Head and Neck Tumors

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Comentario:

Se realizó un estudio por parte de patólogos del hospital Johns Hopkins en el que se identificaron todos los tumores neuroendocrinos (TNEs) de cabeza y cuello diagnosticados en los periodos de enero de 1997 y diciembre de 2017. Se consideraron TNEs de todos los grados histológicos incluyendo adenomas del oído medio, adenoma hipofisario, paraganglioma, carcinoma medular de tiroides, neuroblastoma olfatorio, carcinomas neuroendocrinos y teratocarcinosarcoma nasosinusal.

Se incluyeron 97 TNEs y 626 tumores no neuroendocrinos para observar la expresión inmunohistoquímica de INSM1 (Insulinoma-associated protein 1), el cual es un factor de transcripción que ha surgido recientemente como un marcador de diagnóstico útil de la diferenciación de NE. Expresión INSM1 en la cabeza y el cuello se ha vinculado con el desarrollo del neuroepitelio olfatorio.

INSM1 fue positivo en todos los tipos de los TNEs de cabeza y cuello evaluados en el estudio con una sensibilidad del 99%. En particular, fue positivo en la gran mayoría de las neoplasias malignas NE de alto grado (incluyendo carcinoma neuroendocrino de células pequeñas, de células grandes y teratocarcinosarcoma nasosinusal) y fue negativo en casi todos los tumores no neuroendocrinos con un 97,6% de especificidad (INSM1 fue positivo en solo el 2,4% de los tumores no neuroendocrinos, incluyendo el rabdomiosarcoma alveolar y carcinomas nasosinusales).

Estos hallazgos confirman que INSM1 se puede utilizar como marcador independiente de primera línea de diferenciación neuroendocrina para tumores de cabeza y cuello.

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-24812-3 OPEN

The genomic landscape of 85 advanced neuroendocrine neoplasms reveals subtype-heterogeneity and potential therapeutic targets

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Metastatic and locally-advanced neuroendocrine neoplasms (aNEN) form clinically and genetically heterogeneous malignancies, characterized by distinct prognoses based upon primary tumor localization, functionality, grade, proliferation index and diverse outcomes to treatment. Here, we report the mutational landscape of 85 whole-genome sequenced aNEN. This landscape reveals distinct genomic subpopulations of aNEN based on primary localization and differentiation grade; we observe relatively high tumor mutational burdens (TMB) in neuroendocrine carcinoma (average 5.45 somatic mutations per megabase) with *TP53*, *KRAS*, *RB1*, *CSMD3*, *APC*, *CSMD1*, *LRATD2*, *TRRAP and MYC* as major drivers versus an overall low TMB in neuroendocrine tumors (1.09). Furthermore, we observe distinct drivers which are enriched in somatic aberrations in pancreatic (*MEN1*, *ATRX*, *DAXX*, *DMD* and *CREBBP*) and midgut-derived neuroendocrine tumors (*CDKN1B*). Finally, 49% of aNEN patients reveal potential therapeutic targets based upon actionable (and responsive) somatic aberrations within their genome; potentially directing improvements in aNEN treatment strategies.

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The genomic landscape of 85 advanced neuroendocrine neoplasms reveals subtype-heterogeneity and potential therapeutic targets

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Comentario:

Los tumores neuroendocrinos son un desafío ya que representan un grupo de neoplasias que es heterogéneo en múltiples aspectos: a modo de ejemplo pueden variar en su localización, origen, crecimiento, o incluso en la presencia o ausencia de metástasis al diagnóstico de la enfermedad. Además, resulta complicado su análisis molecular puesto que son genéticamente heterogéneos incluso en muestras que son analizadas en un solo paciente.

En este artículo se aborda la heterogeneidad en mutaciones de 85 tumores neuroendocrinos localmente avanzados y metastásico secuenciados con **tecnología de genoma completo (whole genoma)**. La secuenciación del genoma completo (WGS) es un método que permite obtener toda la información genómica y permite caracterizar las mutaciones que impulsan la progresión del cáncer. Este tipo de análisis revela que existen diferentes subpoblaciones genómicas basadas en la localización primaria y el grado de diferenciación. En este sentido se observan cargas mutacionales relativamente elevadas en el carcinoma neuroendocrino en genes como TP53, KRAS, RB1, CSMD3, APC, CSMD1, LRATD2, TRRAP y MYC, en contraste con los tumores neuroendocrino de bajo grado que presentaron cargas mutacionales bajas. Además, se observó un patrón diferencial de variaciones estructurales somáticas en función de la localización tumoral.

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