Endocrine Abstracts

November/December 2020 Volume 72
ISSN 1479-6848 (online)

18th Annual Meeting of the UK and Ireland Neuroendocrine Tumour Society 2020

30 November – 3 December 2020, Online

UKI NETS 18th National Conference Online
Monday 30 November - Thursday 3 December 2020
Celebrating 20 Years of UKI NETS

published by bioscientifica

Online version available at
www.endocrine-abstracts.org

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18th Annual Meeting of the UK and Ireland Neuroendocrine Tumour Society 2020

Oral Communications

OC1

Identification of soluble immune checkpoint receptor landscape in liver metastases of neuroendocrine neoplasms: A new perspective for immunotherapy

Ewald Doornebal[1,2], Nicola Harris[1], Antonio Riva[1,2], Michail Pizanias[3], Phillips[1,2], Yoh Zen[3], Eva Sticova[3], Andreas Prachalias[3], Krishna Menon[3], Ane Zamalloa[3], Melissa Preziosi[3], Nigel Heaton[3], Simon Eaton[4], John Ramage[3], Roger Williams[1,2], Elena Palma[1,2], Rajaventhan Srirajas, kanthan[2,3]& Shilpa Chokshi[1,2]

[1]Institute of Hepatology, London, United Kingdom. [2]Faculty of Life Sciences & Medicine, King's College London, London, United Kingdom. [3]Institute of Liver Studies, King's College Hospital, London, United Kingdom. [4]University College London, Great Ormond Street Institute of Child Health, Stem Cells & Regenerative Medicine, London, United Kingdom

Accumulating evidence suggests that the immunological landscape plays a key role in the progression of neuroendocrine liver metastases (LM-NENs), which is often characterised by immune cell infiltration. Anti-tumour functions of infiltrating lymphocytes are often silenced through hyper-expression of inhibitory checkpoint receptors (CRs) such as PD-1, but favourable outcomes with anti-PD-1 therapy have been low. Recently, functional soluble (cell-free) CRs beyond PD-1 have been described but their role in LM-NENs is unexplored. Our aim was to characterise soluble CR landscape of LM-NEN patients and examine their expression from the tumour microenvironment using a novel human immuno-competent organotypic tissue slice model for LM-NENs.

We measured plasma levels of stimulatory/inhibitory soluble CRs including sBTLA; sCD27; sCD28; sCD40; sCD80; sCD137; sCTLA-4; sGITR; sHVEM; sIDO-1; sPD-1; sPD-L1; sPD-L2 by multiplex luminex assay in LM-NEN ($n=27$), primary liver cancer ($n=11$), healthy controls ($n=15$). Precision cut tumour slices (PCTS) were prepared from resected LM-NEN tumours ($n=6$) and cultured for up to 15 days. PCTS viability was assessed by measuring ATP, apoptosis (CK18) and lactate dehydrogenase (LDH) release. Proliferative capacity (Ki67) and neuroendocrine differentiation (Chromogranin A) were assessed by immunofluorescence. Immune genes were quantified by microarrays in tumour and peri-tumour tissue. Soluble CR expression was assessed in PCTS supernatants.

A novel and distinct plasma soluble CR signature was observed in LM-NEN patients. We identified ten soluble CRs that were significantly higher compared to healthy controls which interestingly were similar to primary liver cancer. LM-NEN-PCTS were viable for up to 15 days in culture and maintained tissue histoarchitecture, patient specific cellular heterogeneity, neuroendocrine differentiation and mitotic grade compared to the original histopathology of the resected tumour. Immune-specific gene signatures were readily detectable in LM-NEN PCTS, confirming immune infiltration in the tumour microenvironment. LM-NEN-PCTS produced the same soluble CRs signature observed in the plasma.

Soluble checkpoint receptors beyond PD1 are actively involved in LM-NENs offering new insights into the pathogenesis and the development of immunomodulatory therapeutic agents for this cancer. Soluble CRs are actively produced by LM-NET tumour tissue and the PCTS model provides a hitherto unattainable platform for drug development and pre-clinical testing.

*Ewald Doornebal and Nicola Harris are joint first authors

*Rajaventhan Srirajaskanthan and Shilpa Chokshi are joint last authors

DOI: 10.1530/endoabs.72.OC1

OC2

COVID19 & My Care: NCUK community experience

Nikie Jervis & Catherine Bouvier

Neuroendocrine Cancer UK, Leamington Spa, UK

Background

March 2020 saw the UK enter lockdown in response to the global COVID-19 pandemic. The impact on healthcare availability and resources was immediate. To better understand the impact these events had on the Neuroendocrine Cancer community – NCUK undertook a snapshot consultation.

Methods

During May–June 2020, 366 Neuroendocrine Cancer patients across the UK completed an online survey, disseminated via social media and the NCUK patient network.

Results

All responses were from the UK with an even geographical representation and most respondents were linked to a Specialist centre or clinic. In terms of disease site: 57% small bowel primary, 20% pancreatic, 12% lung. More than 50% reported that there had been disruptions to their care: mainly postponed consultations (45%) or postponement of scans (33.7%): not all rescheduled. Significantly, despite media reports, only 3.4% had chosen to delay appointments. Treatment: 18% reported key changes, 17% some changes – 65% reported no change in treatment or treatment plan. Almost 50% reported increased anxiety – due to lockdown and restricted access to specialist care. For 66%, support was received from Specialist Nurses*(40%) and GPs (30%). Of those reporting no support, in the majority of cases (70%) this was patient choice, however 30% said they had no contact details, no response or their point of contact was not available. Most respondents were satisfied with care and understood reasons for delays / changes in care.

Conclusion

This survey offers an insight into the impacts of Covid-19 on the UK Neuroendocrine Cancer Community. What is striking is the significant impact in terms of health anxiety and psychosocial well-being – even for those, who are reasonably well and usually seen less frequently. Whilst it is reassuring to note that many patients have been able to maintain access to healthcare and contact their teams, for others there have been delays and cancellations of appointments, investigations and / or treatments – some with no further plans made, leaving them feeling adrift.

**During peak period – many CNSs were redeployed – NCUK received requests for telephone triage assistance during this time to maintain patient support – which was provided. Respondents did not distinguish between NHS or NCUK Nurse Teams.*

DOI: 10.1530/endoabs.72.OC2

OC3

Omic gene cluster evaluation amplifies the prognostic accuracy of the NETest

Mark Kidd[1], Alexandra Kitz[1], Ignat Drozdov[1] & Irvin Modlin[2]

[1]Wren Laboratories, Branford, USA; [2]Yale University, New Haven, USA

Background

The NETest is a multi-gene assay comprising 51 circulating neuroendocrine tumor specific transcripts. The quotient of the 51-gene assay is based upon multi-algorithmic data analysis. Eight cancer hallmarks or 'omes' (apoptome, epigenome, growth factor signalome, metabolome, proliferome, plurome, secretome SSTRome) represent 29 genes. The NETest is an accurate diagnostic (>90%) but its prognostic utility has not been assessed. In this study, we describe expansion of the NETest omic cluster components and demonstrate that integration amplifies NETest prognostic accuracy.

Methods

Group 1 ($n=222$; including stable disease (SD: $n=164$), progressive disease (PD: $n=76$) and controls ($n=139$)). Group 2: NET Registry #NCT02270567 ($n=88$, prospective samples (SD $n=54$ and PD $n=34$) with up to 24 months follow-up. We used PubMed literature review, interactomic analysis, non-parametric testing, Kaplan-Meier survival curves and Chi^2 analyses to inform and define the prognostic significance of NET genomic 'hallmarks'.

Results

2020 Interactomic analysis: Reassessment of 47 NETest genes identified a further 6 omes: fibrosome, inflammasome, metastasome, NECome, neurome and TFome. *Group 1 analysis*: Twelve omes, excluding the inflammasome and apoptome, were significantly ($P<0.05$, 2.1–8.2-fold) elevated compared to controls. In the PD group, 7 omes (proliferome, NECome, epigenome, SSTRome, neurome, metastasome and fibrosome) were elevated (both expression levels and fold-change >2) versus SD. *Group 2*. All these 7 omes were upregulated. In PD, they were significantly more elevated ($P<0.02$) than SD. The septet (7) omic expression exhibited a 69% prognostic accuracy. The NETest alone was 70.5% accurate. A low NETest (≤ 40) integrated with epigenome/metastasome levels accurately predicted PD (90%). A high NETest (>40) including the fibrosome/NECome predicted PD development within 3 months (100%). Using decision tree analysis to integrate the 4 omes (epigenome, metastasome, fibrosome and NECome) with the NETest score generated an overall prognostic accuracy of 93%.

Conclusions

Reassessment of NETest omic gene cluster analysis identified 5 additional clinically-relevant cancer hallmarks. Identification of 7 omic clusters (septet) provides a molecular pathological signature of disease progression. The integration of the quartet (epigome, fibrosome, metastasome, NECome) and the NETest score yielded a 93% accuracy in the prediction of future disease status.

DOI: 10.1530/endoabs.72.OC3

Poster Presentations

P1

Post-operative NETest scores detect residual NET disease and accurately predicts tumor recurrence in R0

Irvin Modlin[1], Mark Kidd[2], Kjell Oberg[3], Massimo Falconi[4], Pier Luigi Filosso[5], Andrea Frilling[6], Anna Malczewska[7], Ronald Salem[1], Christos Toumpanakis[8], Faidon-Marios Laskaratos[8], Stefano Partelli[4], Matteo Roffinella[5], Claudia von Arx[8], Beata Kos-Kudla[7], Lisa Bodei[9], Ignat Drozdov[2] & Alexandra Kitz[2]

[1]Yale University, New Haven, USA; [2]Wren Laboratories, Branford, USA; [3]University Hospital, Uppsala, Sweden; [4]San Rafaelle IRCCS, Milan, Italy; [5]University of Torino, Turin, Italy; [6]Imperial College, London, United Kingdom; [7]Medical University of Silesia, Katowice, Poland; [8]Royal Free Hospital, London, United Kingdom; [9]Memorial Sloan Kettering Cancer Center, New York, USA

Introduction

Surgery is the only cure for neuroendocrine tumor (NET) disease. R0 resection is critical for successful tumor resection. Early detection of residual disease is key for optimal management. Both imaging and current biomarkers have intrinsic limitations and are largely ineffective up to 3 months post-surgery. NETest, a multigene blood biomarker test, identifies NETs with >90% accuracy. We hypothesized that surgery would decrease NETest levels and that elevated scores post-surgery would detect residual disease (after R1/R2) and could be used to predict recurrence in R0.

Methods

Multicenter evaluation of surgically treated primary NETs ($n=153$). Blood sampling at D0 and POD30. Follow-up including CT/MRI. mRNA quantification by PCR and algorithmic analysis (NETest score: 0–100; normal ≤ 20). Statistics: Mann-Whitney U-test, Chi^2, Kaplan-Meier survival, AUROC. Mean $\pm$ S.E.M.

Results

NET-cohort ($n=153$): 57 pancreatic, 62 small bowel, 27 lung, 4 duodenal, 3 gastric. Surgery: R0 ($n=102$), R1and R2 ($n=51$). Follow-up: mean 14 months (range 3–68). Preop 153/153 NETest-positive (68 ± 28). *R1/R2 Cohort:* Score decreased (73 ± 26 to 52 ± 27). At POD30, 100% were elevated ($P<0.0001$). *R0 Cohort*: POD30 levels decreased from 62 ± 28 to 22 ± 20 ($P<0.0001$). 30% (31/102) remained elevated: 28% lung, 29% pancreas, 27% small bowel and 1/3 gastric. *Recurrence*: By 12 months, 24/31 (74%) with POD30 NETest>20 had image-identifiable recurrence. NETest>20 predicted recurrence with 100% sensitivity and correlated highly ($Chi^2=17.1$, $P<0.0001$) with residual disease. AUROC analysis identified AUC=0.96 ($P<0.0001$) for recurrence-prediction.

Conclusion

A liquid biopsy (NETest) genomic biomarker for neuroendocrine tumors is 100% accurate for tumor diagnosis. All resections decreased NETest levels. NETest>20 at POD30 predicted radiologically recurrent disease with 93% accuracy and 100% sensitivity. R0 resection appears to be ineffective in ~30%. NET mRNA blood levels provide early objective genomic identification of residual disease and may facilitate management.

DOI: 10.1530/endoabs.72.P1

P2

Survey of challenges in access to diagnostics and treatment for neuroendocrine tumor (NET) patients (SCAN) – UK and Ireland vs global diagnosis of NETs

Catherine Bouvier[1,2], Mark McDonnell[1], Christine Rodien-Louw[1], Dirk Van Genechten[1], Simone Leyden[1], Elyse Gellerman[1], Sugandha Dureja[1] & Teodora Kolarova[1]

[1]International Neuroendocrine Cancer Alliance, Boston, USA; [2]Neuroendocrine Cancer UK, Leamington Spa, United Kingdom

Background

Neuroendocrine tumors are uncommon and complex neoplasms with increasing incidence and prevalence worldwide. SCAN assessed global delivery of healthcare to NET patients.

Methods

During Sept-Nov 2019, 2359 NET patients/carers and 436 healthcare professionals (HCPs) from 68 countries completed an online survey, available in 14 languages.

Results

12% NET patients/carers were from United Kingdom (UK) [279/2359], 5% from Ireland (IE) [119/2359]. Almost half of patients had stage IV NETs at diagnosis (Global: 46%[1077/2359]; UK: 45%[126/279]; IE: 41%[49/119]. After initial symptoms and tests, NET was the first diagnosis for about one third of patients (Global: 27%[640/2359]; UK: 28%[79/279]; IE: 35%[41/119]). 44%(1043/2359) of patients globally were initially misdiagnosed at least once with other conditions, this share being significantly higher in UK: 53%(148/279) vs global and IE 39%(46/119) ($P<0.0001$). Mean time to correct diagnosis for those misdiagnosed was aligned: globally 4.75 years ($n=1043$), 4.4 in UK ($n=148$) and 5.24 in IE ($n=46$). The majority of NET patients received their diagnosis at a hospital without a NET specialist (Global: 41%[968/2359]), UK: 45% [125/279]) vs IE: 50% [60/119]), and 19% globally vs. 23% both in UK and IE – in a hospital with a NET specialist. In the UK every fourth NET patient received diagnosis in a medical center specialized in NETs (24%[68/279]), this ratio being significantly lower globally (11%[253/2359]) and in IE (9%[11/119]). The diagnostic tools that most often led to correct diagnosis were biopsy, higher in IE vs UK (Global: 59%[1392/2359]; UK: 54%[150/279]; IE 67%[80/119]) ($P<0.0001$) and CT scan, significantly higher in UK and IE vs global average usage (Global: 45%[1060/2359], UK 58%[162/279], IE 58%[70/119] ($P<0.0001$).

Conclusion

The high proportion of NET patients diagnosed with stage IV, which is associated with poorer patient outcomes, remains a global challenge. The experience of UK and Irish patients on their route to diagnosis is similar to that of the surveyed patients around the world. Access to specialized NET centers should be improved for all NET patients and more healthcare professionals knowledgeable in NETs are needed.

DOI: 10.1530/endoabs.72.P2

P3

Circulating biomarkers to predict progression-free survival in patients with neuroendocrine tumours received ^{177}Lu-DOTATATE

Luohai Chen[1,2], Gopinath Gnanasegaran[1], Dalvinder Mandair[1], Christos Toumpanakis[1], Martyn Caplin[1] & Shaunak Navalkisoor[1]

[1]Royal Free Hospital, London, United Kingdom; [2]The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China

Background

^{177}Lu-DOTATATE is increasingly used in patients with advanced neuroendocrine tumour (NET). However, few circulating biomarkers are available to predict progression-free survival (PFS) of patients received ^{177}Lu-DOTATATE.

Materials and methods

Clinicopathological data and data of baseline circulating biomarkers including neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), erythrocyte sedimentation rate (ESR), creatinine, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, c-reactive protein (CRP), estimated glomerular filtration rate (eGFR) and chromogranin A (CgA) of patients with advanced NET received ^{177}Lu-DOTATATE were retrospectively collected. Continuous variables were normalized by divided them by their upper normal limits (UNL) and classification and regression trees (CART) was used to determine optimal cutoff value. Univariate and multivariate cox regression analysis were used to identify independent biomarkers to predict PFS. Decision curve analysis (DCA) was applied to determine the clinical net benefit of using different biomarkers to guide treatment decision.

Results

195 patients were included. Using CART method, the optimal cutoff value of NLR, normalized ESR, normalized ALP, normalized CRP and normalized CgA to identify patients with shorter PFS were 3, 0.5, 1, 3 and 50 respectively. Multivariate cox analysis indicated that besides primary site of pancreas, only normalized ESR ≥ 0.5, normal baseline creatinine and CgA ≥ 50 were independently associated with shorter PFS. After combining these three risk biomarkers, patients could be divided into three groups with progressively shorter PFS: patients with ≤ 1 risk biomarker (median PFS, 37 months), patients with two risk biomarkers (median PFS, 23 months) and patients with three risk biomarkers (median PFS, 11 months). Subgroup analysis found that risks of progression of these three groups were still significantly different in different subgroup of patients. DCA showed an increased net benefit by using these risk biomarkers to guide treatment decision.

Conclusion

Normalized ESR ≥ 0.5, normal baseline creatinine and CgA ≥ 50 are independently associated with shorter PFS of patients with advanced NET received ^{177}Lu-DOTATATE and can be used to guide treatment decision.

DOI: 10.1530/endoabs.72.P3

P4

Telotristat in the management of Carcinoid diarrhoea – real world experience of patients from an ENETs centre of excellence in Neuroendocrine tumours.

Amardeep Khanna[1,2,3], Nicole Cianci[4], Husnain Abbas Shah[4], Ashish Goel[4], Asma Jebril[4], Jessica Chauhan[4], Michelle Pipe[4], Shishir Shetty[4,5], Christopher Weston[5], Hema Venkataraman[4], Stacey Smith[4], Suzanne Vickrage[4], Joanne Kemp-Blake[4] & Tahir Shah[4]

[1]Institute of Liver Sciences, Kings College Hospital, London, United Kingdom; [2]Liver Unit, Queen Elizabeth Hospital, Birmingham, United Kingdom. [3]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom; [4]University Hospitals Birmingham, Birmingham, United Kingdom; [5]Institute of Immunology and Immunotherapy, Birmingham University, Birmingham, United Kingdom

Carcinoid syndrome occurs in 20% patients, presenting with flushing, abdominal pain, diarrhoea, and wheeze and can be challenging to manage. The standard of care for carcinoid syndrome is somatostatin analogues (SSAs) with add-on Creon, codeine and loperamide therapy. Nonetheless, half of patients experience debilitating diarrhoea. Telotristat-ethyl is a peripheral tryptophan-hydroxylase inhibitor approved for treatment of diarrhoea, supported by Phase 3 clinical trials but lacking in real-world data. Here we present our experience on effectiveness of Telotristat on carcinoid diarrhoea in the largest cohort of patients outside a clinical trial. The primary outcome was reduction in stool frequency (number/day) of >30%, as defined in most studies. Data was collected retrospectively from an electronic database. We included 31 patients (25M, 6F; Median age 69 (45–85) years) {study group} on Telotristat and 10 patients on maximum dose of 2 weekly SSAs but no Telotristat (6M, 4F; Median age 67 (49–79) years) {control group}. The mean (range) duration of treatment in each group was 258 (15–479) and 689 (219–1446) days, respectively. Primary end-point was achieved in 82% (23/28) patients on Telotristat with median-percentage reduction stool frequency of 60% (IQR 50–69), compared to 28% (2/7) (22 (-30 to 55)%) in the control group, (OR-11, 95% CI 1.71–77.1). The pre and post values were compared by Wilcoxon signed rank test. There was a statistically significant change in pre and post stool frequency in Telotristat group {5(3–60) to 2(1–2.5), $P<0.01$}. A significant reduction in Urinary 5-hydroxyindoleacetic acid (5-HIAA) was noted in the Telotristat group ($n=28$) {740 (342–1462) to 334 (125–709) µmol/24 h, $P<0.001$}. Interestingly, change in stool frequency did not correlate with delta HIAA (ρ:027, $P=0.2$). The delta change in stool frequency between the two groups was significant ($P=0.04$). No significant difference ($P=0.185$ (Fisher's exact test)} in mortality was seen between Telotristat {16% (5/31)} and the control group {40% (4/10)}. One patient discontinued Telotristat due to mood changes, which reversed after stopping the drug. In conclusion, our real-world study supports the effectiveness and safety of Telotristat to treat carcinoid diarrhoea in patients not responsive to SSA.

DOI: 10.1530/endoabs.72.P4

P5

Allelic deletion of chromosome 18 is common in intra-abdominal neuroendocrine neoplasms

Shailesh Gohil[1,2], Rob Hastings[1], Jacqui Shaw[1] & Miles Levy[1,2]

[1]University of Leicester, Leicester, United Kingdom; [2]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom

Introduction

Our knowledge of the genomic background of neuroendocrine neoplasms (NENs) is rapidly expanding with more widespread use of sequencing technologies. Although known to be mutationally quiet compared to some other malignancies, many NENs harbour somatic copy number alterations (SCNAs), however the significance of these are unclear.

Aims

We sought to identify SCNAs in a cohort of patients with NENs.

Methods

Whole exome sequencing was performed on DNA extracted from formalin-fixed paraffin embedded tumour samples and matched leucocytes (as a normal germline control), for 9 patients with NENs (6 small intestinal, 1 ovarian, 1 pelvic and 1 lung). Established in-house bioinformatics pipelines were used to identify SCNAs in each tumour DNA sample.

Results

Gene and region specific amplifications and deletions were detected in all patients. Deletion of 1 copy of chromosome 18 was detected in 8 of 9 patients (89%), the exception being the patient with lung carcinoid. Loss of chromosome 9 was observed in 3 patients (2 small intestinal plus ovarian). Gains of chromosome 5 and chromosome 20 ($CN=3$) were observed in 3 patients each (3 small intestinal and 2 small intestinal plus ovarian respectively).

Conclusion

Loss of heterozygosity is common to NENs and in particular loss of chromosome 18 including the *DCC* gene was common in this small cohort of NENs. Previous molecular studies have shown reduced expression of *DCC* in NENs suggesting this as a candidate tumour suppressor in these cancers. Future molecular mechanistic studies on these commonly affected chromosomes may help identify other important genes that drive NEN tumourigenesis.

DOI: 10.1530/endoabs.72.P5

P6

Metachronous neuroendocrine neoplasms in England 2013–2015

Benjamin E White[1], Tracey Genus[2], Catherine Bouvier[3], John K Ramage[1] & Rajaventhan Srirajaskanthan[4]

[1]Hampshire Hospitals NHS Foundation Trust, Basingstoke, United Kingdom; [2]Public Health England, London, United Kingdom; [3]Neuroendocrine Cancer UK, Leamington Spa, United Kingdom; [4]King's College London, London, United Kingdom

Introduction

The aetiology of NENs vary; some are sporadic, others familial. An association between index NENs of the mid gut (ileum and colon) with subsequent colorectal primaries has been reported.

Aim

We determined to evaluate the relationship between the diagnosis of an index primary malignancy and subsequent diagnosis of NEN.

Methods

A population-based retrospective cohort study was under taken for persons with NEN diagnosis in England between 1st January 2013 and 31st December 2015, using data collected by Public Health England National Cancer Registration and Analysis Service (NCRAS). NENs were defined by the WHO 2015 classification, excluding diffuse pulmonary neuroendocrine hyperplasia. All multiple primary malignancies captured from 1965 to present were identified; tumours diagnosed pre-NEN, post-NEN and synchronous. Multiple logistic regression was used to determine the odds ratio to approximate relative risk of those diagnosed with a NEN, by site, in England between 2013 and 2015 being previously exposed to cancer, adjusting for age and sex.

Results

12.844 persons were diagnosed with a NEN in England in the specified time period. Many had multiple primaries; 16.225 tumours were diagnosed in the cohort overall, including NENs and non-NENs (excluding benign tumours and basal cell carcinomas). 2.805 (21.8%) patients had at least one metachronous or synchronous cancer, 81% of which had an index primary before the 2013–2015 diagnosis of a NEN, 12% a primary subsequent to NEN, and 7% with a synchronous other primary. The most common sites for metachronous cancer primaries were prostate (14%), breast (13%), non-melanoma skin cancer excluding Merkel cell carcinomas (12%) and colon (11%). Significant associations were found between many NEN and index primaries: colorectal NEN and prostate, kidney, and testis index primaries; small intestine NENs, prostate and female reproductive organs, kidney and upper GI; and pancreas NEN and kidney, prostate, breast, colorectal, upper GI, thyroid and index primaries.

Discussion

One in five people with NENs may experience secondary malignancies in their lifetime. This association study highlights the requirement for tumour surveillance and counselling of people with NEN. Improvements in cancer registry data will enable survival analysis for longer time periods.

DOI: 10.1530/endoabs.72.P6

P7

Carcinoid heart surgery: Review of outcomes from a single large centre

Rory Maclean[1,2], Jack Cope[1], Shweta Hota[1], Nicola Mulholland[1], John Ramage[1], Olaf Wendler[1] & Raj Srirajaskanthan[1,2]

[1]King's College Hospital, London, United Kingdom; [2]King's College London, London, United Kingdom

Introduction

Up to half of patients with carcinoid syndrome develop carcinoid heart disease; this is thought to be mediated by serotonin from disordered tryptophan metabolism. Valve degeneration can lead to right heart failure which drives morbidity and mortality in this patient population. Surgical replacement of

affected valves is an effective therapy. Peptide receptor radiotargeted therapy (PRRT) has demonstrated better progression-free survival compared to high dose sandostatin LAR.

Methods

We reviewed the clinical records of consecutive patients with carcinoid heart disease who underwent heart valve replacement surgery at a large single centre between 2003 and 2019. Patients were followed up for up to nine years.

Results

26 patients with carcinoid heart disease underwent valve replacement surgery. Mean (S.D.) age was 61 (11) years, 54% female. All had liver metastasis, 31% lymph node, 23% bone and 3.9% lung. CGA at diagnosis mean (S.D.) 600 (1055), HIAA at diagnosis mean (S.D.) 317 (555). NYHA before surgery mean (S.D.) 2.0 (0.7); after surgery mean 1.2; at follow up mean (S.D.) 1.6 (0.8). Mean difference in NYHA score from before to after surgery –0.71 ($P=0.002$). 88.5% had two valves replaced (PR & TR), 3.9% one valve, 3.9% three valves and 3.9% four valves replaced. 13 of 26 patients (50%) received Lutathera PRRT therapy; 27% completed four cycles. All received somatostatin analogues. Mortality at 1, 2, 3, 4, 5 years of follow up was 42%, 50%, 47%, 46%, 50% respectively. In a Cox proportional-hazards model of survival from surgery, adjusting for age (Hazard ratio (HR) 0.96 [0.89, 1.03] ($P=0.25$)), four cycles of Lutathera demonstrated HR 0.087 [0.0079, 0.95] ($P=0.045$) indicating improved survival.

Conclusions

Patients who underwent surgery had relatively early carcinoid heart disease (NYHA II): patients were screened with NT-P-BNP and echocardiography. NYHA symptom scores fell after surgery. All patients received SST analogues, and many received PRRT. Completion of four cycles of Lutathera had a beneficial effect on survival from surgery, although the confidence interval was wide; a randomised controlled trial would be necessary to further determine a treatment effect.

DOI: 10.1530/endoabs.72.P7

P8

The prevalence of depression and anxiety among neuroendocrine tumour and general gastroenterology outpatients and the psychometric validity of emotional thermometers

Kirsty Linton[1], Hannah Newton[1], Sophie Harris[2], Deborah Lancastle[1], Bev John[1], Tracey Vick[1], Janice Rees[3], Rhys Hewett[2], Mohid Khan[2] & Tayyeb Tahor[4]

[1]Department of Psychology, University of South Wales, Cardiff, United Kingdom; [2]Department of Gastroenterology, University Hospital of Wales, Cardiff, United Kingdom; [3]Department of Clinical Psychology, University Hospital of Wales, Cardiff, United Kingdom; [4]Deparment of Liaison Psychiatry, University Hospital of Wales, Cardiff, United Kingdom

Background

Depression and anxiety are frequently associated with functional gastrointestinal disorders (FGID), inducing personal suffering and a decreased quality of life. There is limited data in patients with NETs. Therefore, adequate research identifying the prevalence of these mood disorders among GI patients and NETs are necessary to inform holistic clinical management. Further, due to the nature of hospital clinics being fast-paced, quick and effective screening tools are needed. We aimed to identify the prevalence rates of depression and anxiety among NET and FGID outpatients and to assess the psychometric validity of Emotional Thermometers (ETs) as screening tools for these mood disorders.

Methods

A correlational cross-sectional design was implemented under the 1000-lives-plus methodology for the screening of depression in general gastroenterology clinics. Data was collected from 88 individuals attending FGID and South Wales GEP-NET out-patient clinics via tools consisting of the Patient Health Questionnaire 2 (PHQ-2), PHQ -9 (PHQ-9), the Hospital Anxiety and Depression Scale (HADS) and the Emotional Thermometers (ETs).

Results

Mean age was 54.8. Results indicated that 1 in 2–3 (49.78%) patients met diagnostic criteria of depression and anxiety. Four phases of uncertainty were identified regarding GEP-NET patients, however rates of moderate to severe depression and anxiety were higher among FGID patients (27.59 vs. 9.09, $t = 2.20$; 10.35 vs. 4.55, $t=0.89$). Patients with NETs had a higher prevalence of mild anxiety in comparison to the general gastroenterology clinic (HADS-A) (22.73 vs. 6.90). Further, both multiple and logistic regressions, alongside receiver operating characteristic curves showed only the depression ET to be statistically validated when assessed against the PHQ-9 and HADS.

Conclusion

Depression and anxiety are significant co-morbidities in those with NETs and FGID, often due to the physical and psychological consequences of their illness and delays in diagnosis. Whilst this study holds the strength of being the only research to identify mood disorders within NET populations, it is recommended that future research adopts a longitudinal design, whilst possibly using the current research as a base to build upon.

DOI: 10.1530/endoabs.72.P8

P9

Zoom-ing in on natters: Neuroendocrine cancer UK (NCUK) patient support groups during COVID pandemic

Nikie Jervis & Catherine Bouvier

Neuroendocrine Cancer UK, Leamington Spa, United Kingdom

Background

NHS England's Five Year Forward View refers to peer support as one of the 'slow burn, high impact' interventions that should be seen as 'essential' to the future of healthcare services, with evidence pointing to benefits in both physical and psychosocial well-being of attendees and potential cost savings to healthcare through improved health condition self-management. However the COVID pandemic has meant that groups cannot currently meet face to face. NCUK 'Natter' Support Groups are local community based or regional meetings that offer an opportunity to meet others, who are also affected by Neuroendocrine Cancer. In response to the pandemic, from the start of lockdown, NCUK Natter groups have been offered online via zoom.

Methods

During July to September 2020, NCUK invited its members to complete an online survey – there were 136 respondents.

Results

136 respondents from across the UK: 92% respondents were patients: 62% attended 1 or more meetings with 30% attending >10. Of those who had not attended a face to face group (38%): 20% 'cannot get there'. Most heard about the groups through either NCUK or hospital team (46% and 37% respectively) Reasons for attending: to gain information, meet others/share experiences and support. Key areas of support received: emotional, practical, social and self-care management. Transfer to zoom – only 9% said that they would not join because of format. Asked for preference: 33% would prefer face to face only, however >60% said they would like to have the option of both face to face and zoom. Interestingly respondents would prefer zoom meetings to happen more frequently than face to face. Both formats scored high on attendee experience – criticism reserved for venue, technical issues or timing. 55% reported improvements in physical and psychosocial well-being: improved self-confidence, understanding of diagnosis (tests & treatments), self-management, communication with both family and healthcare teams and reduced isolation.

Conclusion

The results echo reports that peer support is valued by attendees and can benefit their physical and psychosocial wellbeing. Zoom was seen as an ongoing part of peer support. Further study regarding influences for success/failure and reported self-management improvements is recommended.

DOI: 10.1530/endoabs.72.P9

P10

Are outcomes of patients with advanced well-differentiated GEP-NETs on somatostatin analogues similar, irrespective of tracer uptake on ^{68}gallium DOTA SSTR peptide PET CT scans?

Dinakshi Shah[1], Oliver Loveland[1], Amarjot Chander[2], Tom Westwood[2], Prakash Manoharan[2], Was Mansoor[1], Angela Lamarca[1,3], Richard A Hubner[1,3], Juan W Valle[3,1] & Mairéad G McNamara[3,1]

[1]Medical Oncology, The Christie NHS Foundation Trust, Manchester, United Kingdom; [2]Nuclear Medicine, The Christie NHS Foundation Trust, Manchester, United Kingdom; [3]Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom

Background

Neuroendocrine tumours (NETs) are a rare and heterogeneous group of neoplasms that mainly originate from the gastroenteropancreatic tract (GEP-NETs). The vast majority of NETs tend to overexpress somatostatin receptors (SSTRs), which can be targeted by somatostatin analogues (SSAs). ^{68}Gallium DOTA SSTR peptide positron emission tracer computed tomography (^{68}Ga PET-CT) has emerged as superior to other imaging modalities in identifying SSTRs. This study aimed to assess whether patients with GEP- NETs treated with SSAs have similar outcomes irrespective of tracer uptake intensity on ^{68}Ga PET-CT.

Methods
Patient cases undergoing ^{68}Ga PET-CT imaging between November 2015 and September 2020 at The Christie NHS Foundation Trust, with diagnosis of histologically-confirmed advanced GEP-NETs receiving SSAs, were reviewed retrospectively. Kaplan-Meier and Cox regression were utilised to analyse progression free (PFS) and overall survival (OS).
Results
Of 644 patients imaged with ^{68}Ga PET-CT, 132 met inclusion criteria. The median age of patients was 62 years; ECOG performance status 0: 62 (47%), 1: 56 (42%), 2: 13 (10%); primary sites: ileum: 54 (41%), pancreas: 26 (20%), cancer of unknown primary: 20 (15%), Grade (G)1: 63 (47%), G2: 56 (42%), G3: 3 (2%), unknown: 11 (8%); ^{68}Ga PET-CT tracer uptake increased: 124 (94%), no increased tracer uptake: 8 (6%). 66 patients (50%) progressed, and 99 (74%) were alive at analysis. Median PFS on SSAs was 20.82 months (95% confidence interval (CI) 12.2–30.03) for patients with increased tracer uptake ($n=63$) and 8.26 months (95% CI 4.55-not available (NA)) for patients with no increased tracer uptake ($n=3$) (Hazard Ratio (HR): 4.19 (95% CI 1.238–14.28), $P=0.022$). Median OS from commencement of SSA was: 99.51 months (95% CI 95.96 – NA) for patients with increased tracer uptake and 47.67 months for patients with no increased tracer uptake (95% CI 13.41 – NA) (HR 2.93 (95% CI 1.011–8.49), $P=0.048$).
Conclusions
^{68}Ga PET-CT scans are an accurate tool for diagnosis and localisation of NETs. Median PFS and OS appears to be greater in patients receiving SSAs with increased uptake on the ^{68}Ga PET-CT. However, further evaluation in larger cohorts is needed to definitively assess clinical benefit of SSAs in the ^{68}Ga PET-CT negative cohort.

DOI: 10.1530/endoabs.72.P10

P11

The discontinuation of interferon-alfa for the treatment of metastatic NET: A case amongst many of poorer patient outcomes?

Ricky Fenn, Alexander Pawsey & Gaurav Kapur
Norfolk and Norwich University Hospital, Norwich, United Kingdom

Interferon alfa-2a was discontinued in June 2020. Here we present a case of an unfortunate patient for whom this change has dramatically impacted the course of her illness. A 64-year-old woman initially presented in 2007 with refractory hypertension and was found to have a phaeochromocytoma which was resected. Metastatic recurrence of her disease in the liver and vertebrae was confirmed by CT/MRI in 2014 following rising catecholamines on monitoring. Her MIBG scan in early 2015 revealed no uptake. Whilst on phenoxybenzine, somatostatin-analogues and cyclophosphamide, vincristine and dacarbazine over the next two years her disease continued to progress both on imaging and biochemical markers. Her quality of life had deteriorated to WHO performance status 3. She started on Interferon alfa-2a in June 2017 (repeat MIBG scan again showed no uptake). Her disease stabilised from this point and her biochemical markers normalised. Her performance status improved and she had a good quality of life for two years with stable disease on her scans up to June 2020. Interferon alfa-2a became unavailable from March 2020 due to the manufacturer discontinuing production and patients were started on Peginterferon as an alternative. From June 2020 our patient's metanephrines began rising quickly and CT scans showed hepatic disease progression. This was followed with an admission (August 2020) with uncontrolled hypertension and falls from orthostatic hypotension. Despite significant input and medication management between oncology and endocrinology teams she was discharged with increased care and a reduced prognosis. This has remained an issue and her quality of life is greatly reduced. Quick review of the disease course of our patients (4 total) on Peginterferon revealed a 72-year-old with a metastatic small bowel NET previously stable on Interferon alfa-2a now progressing on a CT scan in August 2020 since switching. Other patients' diseases remained stable or were not comparable to our case. This case illustrates the detrimental impact the discontinuation of drugs which may not be considered viable by the industry, but have a significant impact on survival and QOL. Discontinuation of this drug deprived a small proportion of patients with NETs a valuable and important treatment.

DOI: 10.1530/endoabs.72.P11

P12

A new diagnosis of both a pituitary TSH-oma and a metastaticneuroendocrine tumour

Hessa Boharoon, Mustafa Al Ansari, Rohini Sharma, Vasiliki Bravis & Florian Wernig
Imperial NHS, London, United Kingdom

We report a new diagnosis of a pituitary TSH-oma together with a metastaticneuroendocrine tumour. A 61 year old man presented with a 3-year history of diarrhoea. His past medical history includes paroxysmal atrial fibrillation, for which he has had an ablation in the past. He takes no regular medications. Initial investigations were suggestive of hyperthyroidism in the context of unusual thyroid function test results (elevated freeT4 and freeT3 with elevated TSH). A pituitary MRI revealed a pituitary macroadenoma, measuring 1.5 cm in size. Whilst being investigated for a possible TSH-oma, due to the presence of flushing alongside his diarrhoea, two 24 urinary 5-HIAA samples were sent, both of which returned elevated. Chromogranin A was also elevated, and he underwent a Gallium DOTATATE PET CT scan which was suggestive of a metastatic neuroendocrine tumour with metastatic spread to the liver, the bones, the peritoneum as well as focal indeterminate cardiac septal activity. A liver biopsy confirmed a grade-1 neuroendocrine tumour with a Ki-67 labelling index of 1%. Cardiac MRI confirmed myocardial neuroendocrine tumour involvement. The patient was commenced on somatostatin analogues which normalised his thyroid function tests. In view of his bone metastases, he was also started on denosumab. In view of him having two rare conditions, he has been referred for genetic testing although he has no family history of similar conditions. To our knowledge, this is the first reported case of a coexisting TSH-oma and a metastatic neuroendocrine tumour. Whether there is a genetic link between those two rare pathologies or whether they occurred coincidently remains to be seen.

DOI: 10.1530/endoabs.72.P12

P13

Well-differentiated Gastroenteropancreatic G3 NET: Findings from a large single centre cohort

Kirstie Lithgow[1], Hema Venkataraman[2], Simon Hughes[2], Husnain Shah[2], Joanne Kemp-Blake[2], Suzanne Vickrage[2], Stacey Smith[2], Sian Humphries[2], Mona Elshafie[2], Philipe Taniere[2], Salvador Diaz-Cano[2], Bobby Dasari[2], Max Almond[2], Sam Ford[2], John Ayuk[2], Shishir Shetty[2], Tahir Shah[2] & Ian Geh[2]
[1]Cumming School of Medicine, Calgary, Canada; [2]University of Birmingham NHS Foundation Trust, Birmingham, United Kingdom

Purpose
Neuroendocrine neoplasms are known to have heterogeneous biological behavior. G3 neuroendocrine tumours (NET G3) are characterized by well-differentiated morphology and Ki67>20%. The prognosis of this disease is understood to be intermediate between NET G2 and neuroendocrine carcinoma (NEC). Clinical management of NET G3 is challenging due to limited data to inform treatment strategies.
Methods
We describe clinical characteristics, treatment, and outcomes in a large single centre cohort of patients with gastroenteropancreatic NET G3. Data was reviewed from 26 cases managed at our institution from 2012 to 2019.
Results
Most commonly the site of the primary tumour was unknown and majority of cases with identifiable primaries originated in the GI tract. Majority of cases demonstrated somatostatin receptor avidity. Median Ki67 was 30%, and most cases had stage IV disease at diagnosis. Treatment options included surgery, somatostatin analogs (SSA), and chemotherapy with either platinum-based or temozolomide-based regimens. Estimated progression free survival was 4 months following initiation of SSA and 3 months following initiation of chemotherapy. Disease control was observed following treatment in 5/11 patients treated with chemotherapy. Estimated median survival was 19 months; estimated one year survival was 60% and estimated 2 year survival was 13%.
Conclusions
NET G3 is a heterogeneous group of tumours and patients which commonly have advanced disease at presentation. Prognosis is typically poor, though select cases may respond to treatment with SSA and/or chemotherapy. Further study is needed to compare efficacy of different treatment strategies for this disease.

DOI: 10.1530/endoabs.72.P13

P14

Effective multimodality therapy for a metastatic insulin-secreting pancreatic neuroendocrine tumour (NET): A case report

Jonathan Ting[1], Matthaios Kapiris[1], Andreas Prachalias[2], Anand Velusamy[3], Barbara McGowan[3], Paul Carroll[3], Rosa Miquel[2], Kiruthikah Thillai[1] & Debashis Sarker[1,4]

[1]King's Health Partners ENETS Centre of Excellence, Department of Medical Oncology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [2]Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom; [3]Department of Endocrinology, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [4]School of Cancer and Pharmaceutical Sciences, King's College London, London, United Kingdom

A 23-year-old woman presented in May 2018 with acute left-sided hemiparesis following increasingly frequent episodes of morning drowsiness with associated weight loss. She had no significant past medical history or family history. Brain imaging excluded intracranial pathology. Blood tests during a spontaneous hypoglycaemic episode (1.5 mmol/l) identified significant hyperinsulinaemic hypoglycaemia [insulin 392 pmol/l (18–173) and C-peptide 3913 pmol/l (370–1470)]. MRI and ^{68}Ga-DOTATATE-PET identified a somatostatin receptor avid pancreatic tail mass with liver metastases in segments VII/VIII and III, and a subsequent liver biopsy confirmed a well-differentiated NET (Ki-67 1%) with positive MNF116, CD56, synaptophysin and chromogranin expression. Hypoglycaemia was initially refractory to diazoxide and daily TDS octreotide therapy, and continuous 20% dextrose infusions were required to maintain normoglycaemia. Following discussion at a specialist neuroendocrine multidisciplinary meeting, she proceeded to have five cycles of Everolimus with neo-adjuvant intent together with dexamethasone and lanreotide, resulting in both rapid restoration of normoglycaemia and a radiological response suitable for one-stage surgical resection. She underwent distal pancreatectomy, splenectomy and anatomical resections of metastases in segments VII, VIII and III in November 2018, and subsequent histology confirmed a well-differentiated grade 2 NET (Ki-67 3%; final staging: pT2N1M1R0 with vascular invasion). Normoglycaemia was sustained after immediate post-operative cessation of medical therapy and no adjuvant therapy was required. No pathogenic germline variants in *MEN1, CDKN1B* and *AIP* were identified, and interval MRI/PET imaging has thus far shown no evidence of recurrence.

Summary

This case identifies a rare early-onset sporadic presentation of a large-volume metastatic insulin-secreting pancreatic NET. Multimodality therapy with somatostatin analogues, corticosteroids and the mTOR inhibitor Everolimus were administered with successful restoration of normoglycaemia despite initial lack of symptomatic response with diazoxide and octreotide. Everolimus was also given with neo-adjuvant intent, leading to a radiological response and subsequent curative surgical resection. Streptozocin-based chemotherapy was initially considered for this patient, however Everolimus was preferred due to the low proliferation index. This case also highlights the symptomatic burden associated with metastatic hormone-secreting NETs, and it is clear that early and ongoing multidisciplinary involvement is required in order to achieve optimal symptom control and treatment outcomes.

DOI: 10.1530/endoabs.72.P14

P15

Specialist dietetic input in the south wales NET clinic: Patient outcomes

Charlotte Dowd, Catherine Powell, Rebecca Taylor, Kathryn Cook, Jennifer Blackhouse & MS Khan

Cardiff and Vale University Health Board, Cardiff, United Kingdom

Background

Nutritional data in NETs is lacking. There are a range of gastrointestinal issues which can be related to the NET, treatment, surgical intervention, or pre-existing diseases[1]. Many of these can have nutritional consequences or be improved through altering diet with the support of a specialist dietitian.

From October 2018, a gastrointestinal specialist dietitian joined the weekly clinic for 12 months. The aim of the service evaluation was to assess the impact of dietetic input on patient outcome data.

Methods

This was a service evaluation. Referrals were assessed by the NET dietitian and outcomes were selected using a dietetics outcome framework. Patients were reviewed in clinic or on a telephone consultation. Statistical tests were unable to be used due to the number of patients seen.

Results

35 patients had outcome measures identified and reviewed over the 12 months. 78% of total outcomes were achieved, 4% were partially achieved and 18% not achieved.

Discussion

The results of this show that outcomes were achieved or partially achieved by most patients. From the results of this service evaluation, and the common nutrition-related problems that patients with NETs encounter, dietetics should be a core member of the MDT to improve patients' outcomes, quality of life and to allow specialist dietetic intervention.

Conclusion

Specialist dietetic input as part of a NET MDT should be recommended as it is effective at improving patients' symptoms and nutritional status.

Reference

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DOI: 10.1530/endoabs.72.P15

P16

Mixed neuroendocrine-non-endocrine neoplasms (MiNEN): A case of pancreatic acinar – neuroendocrine carcinoma of large cell type

Emilie Clifton[1], Christina Karampera[1], Yoh Zen[2], Kiruthikah Thillai[1] & Debashis Sarker[1,3]

[1]King's Health Partners ENETS Centre of Excellence, Department of Medical Oncology, Guy's Hospital, London, United Kingdom; [2]Institute of Liver Studies, King's College Hospital, London, United Kingdom; [3]School of Cancer and Pharmaceutical Sciences, King's College London, London, United Kingdom

Background

MiNEN are a rare histological subgroup defined by the association of at least two morphologically different neoplastic components, including one neuroendocrine. The diagnosis and therapeutic management of MiNEN is considered challenging resulting from the rarity and heterogeneity of this subgroup.

Case

We present the case of a 68-year-old Caucasian male who attended the emergency department with symptomatic hypoglycaemia on a background of poorly controlled type 2 diabetes, weight loss and constipation. ECOG performance status was 2. A CT scan revealed a pancreatic tail mass with extensive bilobar liver metastases, the largest of which was in segment 5 measuring 6x4 cm. A liver biopsy revealed a high grade mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN), consisting of acinar cell carcinoma and a focus of neuroendocrine carcinoma (NEC) of large cell type. The acinar cell carcinoma was suspected more predominant than the neuroendocrine component. Immunostaining was diffusely positive for CK7 and bcl10; chromogranin, synaptophysin and trypsin were moderately expressed. CEA, CD56, CA19–9 and p53 were negative; Ki67 was >70% in hot spots. 68Ga-DOTATATE PET/CT scan showed no sites of increased uptake. As per specialist NET multidisciplinary meeting and in the absence of specific guidelines, he was treated with gemcitabine (due to the predominant acinar component) and cisplatin (given the focal high grade NEC component). Dose modifications were required based on the borderline performance status and thrombocytopenia secondary to splenomegaly due to tumour related splenic vein compression. Following the first cycle of chemotherapy, he continued to deteriorate and was deemed unfit for further chemotherapy and was managed with best supportive care. He died only 3 months from initial diagnosis.

Conclusion

MiNEN is a rare entity which requires timely and accurate diagnosis. This case highlights the inadequacy of relevant clinical evidence, the difficulties associated with determining optimal therapeutic approaches and the poor prognosis associated with high grade MiNEN. The identification of genomic markers to define the molecular heterogeneity of MiNEN will be essential for the development of targeted treatments and prediction of patient outcomes.

DOI: 10.1530/endoabs.72.P16

	G1- Symptom Management	G2- Improve Nutrition	G3- Confirm Nutritional Adequacy	G5- Maintain/ Monitor Nutrition	G6- Empower to Self-manage Condition	G7- Avoid Inappropriate Intervention
Not Achieved	6	0	1	3	6	0
Partially Achieved	0	1	0	0	2	0
Achieved	19	11	5	13	20	0

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