Current practice in approaching controversial diagnostic and therapeutic topics in gastroenteropancreatic neuroendocrine neoplasm management. Belgian multidisciplinary expert discussion based on a modified Delphi method

P.-J. Cuyle[1], K. Geboes[2], S. Carton[1], V. Casneuf[3], J. Decaestecker[4], M. De Man[2], G. Demolin[5], C. M. Deroose[6], C. De Vleeschouwer[7], P. Flamen[8], A. Hendlisz[9], A. Hoorens[10], J. Janssens[11], I. Karfis[8], W. Lybaert[12], G. Machiels[9], E. Monsaert[13], I. Sinapi[14], E. Van Cutsem[15], T. Vandamme[16], I. Borbath[17], C. Verslype[15]

(1) Gastroenterology/Digestive Oncology, Imelda General Hospital, Bonheiden, Belgium ; (2) Gastroenterology, Digestive Oncology, Ghent University Hospital, Ghent, Belgium ; (3) Gastroenterology/Digestive Oncology, OLV Hospital, Aalst, Belgium ; (4) Gastroenterology/Digestive Oncology, AZ Delta Hospital, Roeselare, Belgium ; (5) Gastroenterology/Digestive Oncology, Centre Hospitalier Chrétien St-Joseph, Liège, Belgium ; (6) Nuclear Medicine, University Hospitals Leuven, Leuven, Belgium ; (7) Gastroenterology/Digestive Oncology, Mariaziekenhuis Noord-Limburg, Pelt, Belgium ; (8) Nuclear Medicine, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium ; (9) Medical Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium ; (10) Pathology, Ghent University Hospital, Ghent, Belgium ; (11) Gastroenterology/Digestive Oncology, AZ Turnhout, Turnhout, Belgium ; (12) Medical Oncology, AZ Nikolaas, Sint-Niklaas, Belgium ; (13) Gastroenterology/Digestive Oncology, AZ Maria Middelares, Ghent, Belgium ; (14) Medical Oncology, Grand Hôpital de Charleroi, Charleroi, Belgium ; (15) Digestive Oncology, University Hospitals Leuven, Leuven, Belgium ; (16) NETwerk, Antwerp University Hospital, Edegem, Belgium ; (17) Gastroenterology/Digestive Oncology, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

Abstract

Background and study aims **: Neuroendocrine neoplasms (NENs) are relatively rare, with marked clinical and biological heterogeneity. Consequently, many controversial areas remain in diagnosis and optimal treatment stratification for NEN patients. We wanted to describe current clinical practice regarding controversial NEN topics and stimulate critical thinking and mutual learning among a Belgian multidisciplinary expert panel**

Patients and methods **: A 3-round, Delphi method based project, coordinated by a steering committee (SC), was applied to a predefined multidisciplinary NEN expert panel studying the following controversial topics : factors guiding therapeutic decision making, the use of somatostatin analogues (SSA) in adjuvant setting, the interference between non-radioactive and radioactive SSAs, challenging small intestine neuroendocrine tumor (NET) cases, the approach of the carcinoid syndrome, the role of chemotherapy in well differentiated NET, the relevance of NET G3 and neuroendocrine carcinoma subclassification and the role of imaging techniques in NEN management.**

Results **: A high level of consensus exists regarding the necessary diagnostic work-up, use of imaging techniques and interference between non-radioactive and radioactive SSAs. However, the prognostic impact of tumor functionality might be overrated and adequate diarrhea differential diagnostic work-up in these patients is underused. Significant differences are seen between individual experts and centers regarding treatment preferences both on the treatment modality level, as well as the choice of specific drugs (e.g. chemotherapy regimen).**

Conclusions **: A Delphi-like multi-round expert discussion proves useful to boost critical thinking and discussion among experts of different background, as well as to describe current clinical practice and stimulate mutual learning in the absence of high-level scientific guidance.** (Acta gastroenterol. belg., **2020**, 83, **643-653**).

Keywords : neuro-endocrine tumor, neuroendocrine carcinoma, multidisciplinary team (MDT).

Introduction

Neuroendocrine neoplasms (NEN) are a highly heterogenous group of neoplasms arising from the diffuse neuroendocrine system, originating within the gastroenteropancreatic system in 60 to 70% of cases (1). The most common primary sites for gastroenteropancreatic neuroendocrine neoplasms (GEPNEN) are stomach, small intestine (si), appendix, rectum, pancreas (p) and colon. NENs are classified according to differentiation grade and proliferation index (Ki-67%). Well differentiated NENs are called neuroendocrine tumors (NET) and are subdivided into WHO grade 1 (Ki-67 <3%), WHO grade 2 (Ki-67 between 3-20%) and WHO grade 3 (Ki-67 > 20%) (2). Poorly differentiated NENs are termed neuroendocrine carcinoma (NEC), usually exhibiting aggressive clinical behavior and a high Ki-67 (often above 70%), and are subdivided in large-cell or small-cell neuroendocrine carcinomas on histology. A spectrum of therapeutic approaches with proven anti-tumor activity can be considered, mainly consisting of locoregional approaches (surgery, ablation techniques and bland-, chemo- or radio-embolization techniques), somatostatin analogues (SSA), targeted agents (e.g. everolimus, sunitinib, lenvatinib, surufatinib, pazopanib, cabozantinib), cytotoxic chemotherapy and peptide receptor radionuclide therapy (PRRT) (3). However, guidance on optimal sequencing of therapy is scarce and predictive biomarkers are largely lacking. As a consequence, many areas of controversy remain and therapeutic preferences often differ significantly between countries and individual expert centers. The Delphi technique is a well described, structured process for decision making, using a series of questionnaires or 'rounds' to gather information in an anonymized fashion and usually striving towards reaching a consensus (4). In this paper we describe a modified Delphi study among

Correspondence to : Pieter-Jan Cuyle, Department: Gastroenterology, Digestive Oncology Institute, University Hospital, Imelda General Hospital, Imeldalaan 9, Bonheiden, Antwerp, 2820, Belgium.
E-mail: pieter-jan.cuyle@imelda.be

Submission date : 23/05/2020
Acceptance date : 22/07/2020

a Belgian multidisciplinary expert panel as a vehicle to boost critical thinking and expert discussion on current clinical practice regarding controversial topics within NEN diagnosis and treatment.

Materials and methods

Steering committee

The steering committee (SC), coordinating this Delphi-based expert discussion in an independent manner, consisted of 3 gastroenterologists, specialized in digestive oncology and neuroendocrine neoplasm management (Cuyle PJ, Borbath I, Verslype C). The SC members were responsible for predefining the expert panel setup and -the panelists' desired level of experience and expertise. They selected the topics discussed, created the content of the questionnaires, performed the data analysis and prepared and moderated the round 3 scientific meeting, as well as final outcome reporting. The SC members did not answer round 1 and 2 questions and are therefore not represented in the results shown in the tables and figures.

Panelists

Selection of the participating NEN experts was based on a national level, applying predefined criteria, requiring at least 5 years (y) of prior NEN treatment experience and an individual minimal case load of at least 10 NEN cases per year. The SC aimed to include a variety of medical specialties and some degree of balance in geographical and hospital (academic vs. non-academic) background.

Modified Delphi method

For this research, a modified Delphi process was used to investigate common daily practice regarding challenging and controversial topics within NEN management. The primary aim of the project was to inquire on the use of a Delphi method as a suitable way of stimulating critical reflection and discussion among experts, rather than striving towards consensus. The Delphi-like process was performed over a 9-month period and was set up as a 3-round project. An independent third-party vendor was appointed for hosting and processing the online questionnaires, as well as anonymizing the gathered data. The SC decided which topics were withheld throughout the first 2 rounds into the open discussion in round 3, mainly focusing on the most controversial ones. The topics finally examined and reported on in this manuscript included : factors guiding therapeutic decision making, the use of SSA in adjuvant setting, the interference between radioactive and non-radioactive SSA's, challenging siNET cases, the approach of the carcinoid syndrome, the role of chemotherapy in well differentiated NET, the relevance of NET G3 and NEC subclassification and the role of imaging techniques in NEN management.

The first round was an electronic 'open question formula' questionnaire, addressing 12 main topics and consisting of 43 sub-questions in total. Answers were analyzed by the SC and used to develop the second round questionnaire. As there was no desire to seek consensus, no feedback on any of the round 1 results was given to the panelists. The second questionnaire contained 9 main topics and was built as a mix of (optimally rephrased) open questions and multiple choice questions using the round 1 open question answers as different options. This was done to really push the participants into stating their personal preference as much as possible. At the end of round 2 the SC analyzed the data and calculated the consensus level for all topics based on the predefined definition of consensus. The third round was an interactive face-to-face meeting for which panelists were invited (without obligation). The meeting was moderated by the SC members, presenting the round 1 and 2 results and creating an open discussion amongst the participating NEN experts on all investigated topics. The SC members used the – in their opinion - more controversial answers or motivations, collected during round 1, to fuel this discussion when necessary. Round 3 included a re-voting on two topics by means of the SurveyGizmo® tool, in which the SC members could participate. The exact questions and respective answers are presented in the text, tables and figures below.

Consensus definition

A 75% agreement level was identified as minimum threshold for consensus in analogy to many Delphi consensus method guidelines (5).

Statistical analysis

Results are presented in a descriptive fashion. Percentages for each answer were computed using the total number of participants that answered that (sub) question as a denominator. If a certain answer field, for whatever specific reason, was left blank, that participant was not included in the denominator for percentage calculation. No statistical analysis was performed.

Role of the funder

Novartis introduced the concept of organizing a modified Delphi panel on neuroendocrine neoplasms to the members of the steering committee. XPE-Pharma & Science was used as an independent vendor creating the electronical platform for online completion of round 1 and 2 questionnaires by the panelists and providing anonymized feedback of the answers to the steering committee. Novartis provided financial support through honoraria for the steering committee members and panelists and provided logistic support for the round 3 meeting. Although steering committee members and panelists were not blinded to the funder of this Delphi

panel, Novartis was not involved in the selection of panel experts, the choice of topics discussed, the interpretation of the data nor the compilation and content of the final manuscript.

Results

Panelists demographics

Of the 55 physicians originally invited by email, only 19 met the panel inclusion criteria and agreed to participate. The panel consisted of 11 digestive oncology specialists (57.9%), 4 general oncology specialists (21%), 3 nuclear medicine specialists (15.8%) and one pathologist (5,3%). Mean number of years of prior experience treating NEN was 17.3y (median 14y ; range 7-32y) and mean number of individual NEN patients treated per year was 72.1 (median 30 ; range 12-600) (table 1).

Due to administrative reasons, 2 physicians from the original 19 were not able to participate in the first round. They joined in from the second round onwards. One participant did not complete round 1 and 2- questionnaires and was excluded from the analysis. Response rate at round 1 was 100% (16/16) and 94.4% (17/18) at round 2. Round 3 participation level was 63.2% (12/19).

Table 1. — **Panelist demographics (n=19)**

Case load/year	Experience (years)	Experience according to case load
12	17	**Case load < 25/year (n=5)**
12	8	range (y) 8 to 20
15	10	mean (y) 13,8
20	20	median (y) 14,0
20	14	
30	13	**Case load 25 to 50/y (n=7)**
30	30	range (y) 10 to 32
30	15	mean (y) 17,6
30	11	median (y) 13,0
30	10	
30	32	**Case load 50 to 100/y (n=3)**
40	12	range (y) 14 to 31
50	31	mean (y) 23,3
50	14	median (y) 25,0
70	25	
100	14	**Case load ≥100/y (n=4)**
100	25	range (y) 7 to 25
100	7	mean (y) 16,5
600	20	median (y) 17,0

Topic 1 – Impact of NEN characteristics in clinical practice

During round 1, the expert panel was asked to provide a list of NEN characteristics needed to guide their therapeutic decision making in daily practice. The

Table 2. — **Which of the following characteristics guide your therapeutic decision making in GEPNEN?**

	YES	***NO***
1. TNM-stage (n=18)	**100%** (18/18)	-
2. Hereditary syndrome (n=18)	66.7% (12/18)	33.3% (6/18)
3. Tumor functionality (n=18)	**94.4%** (17/18)	5.6% (1/18)
4. Functional imaging (n=18)	**100%** (18/18)	-
5. Tumor differentiation (including Ki-67%) (n=18)	**100%** (18/18)	-
6. Serum chromogranine A (n=18)	38.9% (7/18)	61.1% (11/18)
7. Primary tumor location (n=18)	**94.4%** (17/18)	5.6% (1/18)
8. Patient related factors (n=18)	**100%** (18/18)	-
9. Therapy availability (n=17)	**94.1%** (16/17)	5.9% (1/17)
10. Patient preference (n=18)	**88.9%** (16/18)	11.1% (2/18)

GEPNEN : gastroenteropancreatic neuroendocrine neoplasm. This table contains the round 2 results. Bold characters are used when a consensus (≥ 75% of experts agreed or disagreed on a parameter) is obtained.

Table 3. — **Which of the following characteristics have prognostic value when treating GEPNEN patients?**

	YES	***NO***
1. TNM-stage (n=18)	**100%** (18/18)	-
2. Hereditary syndrome (n=18)	61.1% (11/18)	38.9% (7/18)
3. Tumor functionality (n=18)	**83.3%** (15/18)	17.7% (3/18)
4. Functional imaging (n=18)	**88.9%** (16/18)	11.1% (2/18)
5. Tumor differentiation (including Ki-67%) (n=18)	**100%** (18/18)	-
6. Serum chromogranine A (n=18)	38.9% (7/18)	61.1% (11/18)
7. Primary tumor location (n=17)	**88.2%** (15/17)	11.8% (2/17)
8. Patient related factors (n=18)	**88.9%** (16/18)	11.1% (2/18)
9. Therapy availability (n=18)	44.4% (8/18)	55.6% (10/18)
10. Patient preference (n=18)	44.4% (8/18)	55.6% (10/18)
11. Carcinoid heart disease (n=17)	**100%** (17/17)	-
12. Tumor molecular features (n=18)	**77.8%** (14/18)	22.2% (4/18)

GEPNEN: gastroenteropancreatic neuroendocrine neoplasm. This table contains the round 2 results. Bold characters are used when a consensus (≥ 75% of experts agreed or disagreed on a parameter) is obtained.

Table 4. — **Rank your top 5 of prognostic features according to their importance in pNET**

	1st choice (n=18)	2nd choice (n=18)	3rd choice (n=18)	4th choice (n=18)	5th choice (n=18)
1. Staging	50% (9/18)	38.9% (7/18)	-	-	-
2. Grading	44.4% (8/18)	38.9% (7/18)	16.7% (3/18)	5.5% (1/18)	-
3. SSTR-imaging	5.6% (1/18)	-	33.4% (6/18)	16.7% (3/18)	11.1% (2/18)
4. ^{18}F-FDG-PET imaging	-	22.2% (4/18)	22.2% (4/18)	22.2% (4/18)	11.1% (2/18)
5. ATRX/DAXX mutation	-	-	5.5% (1/18)	5.5% (1/18)	27.9% (5/18)
6. Hormone related symptoms	-	-	16.7% (3/18)	27.9% (5/18)	5.5% (1/18)
7. Serum chromogranine A	-	-	5.5% (1/18)	-	5.5% (1/18)
8. Tumor related symptoms	-	-	-	16.7% (3/18)	33.4% (6/18)
9. Carcinoid heart disease	-	-	-	5.5% (1/18)	5.5% (1/18)

pNET : pancreatic neuroendocrine tumor ; SSTR: somatostatin receptor ; ^{18}F-FDG-PET : ^{18}F-fluorodeoxyglucose positron emission tomography ; ATRX : transcriptional regulator ATRX also known as ATP-dependent helicase ATRX ; DAXX : death-domain associated protein 6. This table contains the round 2 results.

Table 5. — **Rank your top 5 of prognostic features according to their importance in siNET**

	1st choice (n=18)	2nd choice (n=18)	3rd choice (n=18)	4th choice (n=18)	5th choice (n=18)
1. Staging	55.5% (10/18)	22.2% (4/18)	-	5.5% (1/18)	-
2. Grading	38.9% (7/18)	38.9% (7/18)	11.1% (2/18)	11.1% (2/18)	-
3. SSTR-imaging	-	16.7% (3/18)	22.2% (4/18)	22.2% (4/18)	11.1% (2/18)
4. ^{18}F-FDG-PET imaging	5.6% (1/18)	11.1% (2/18)	16.7% (3/18)	11.1% (2/18)	27.9% (5/18)
5. ATRX/DAXX mutation	-	-	-	-	-
6. Hormone related symptoms	-	5.6% (1/18)	11.1% (2/18)	16.7% (3/18)	5.5% (1/18)
7. Serum chromogranine A	-	-	5.6% (1/18)	-	5.5% (1/18)
8. Tumor related symptoms	-	-	-	22.2% (4/18)	22.2% (4/18)
9. Carcinoid heart disease	-	5.6% (1/18)	33.3% (6/18)	11.1% (2/18)	27.8% (5/18)

siNET : small intestine neuroendocrine tumor ; SSTR : somatostatin receptor ; ^{18}F-FDG-PET : ^{18}F-fluorodeoxyglucose positron emission tomography ; ATRX : transcriptional regulator ATRX also known as ATP-dependent helicase ATRX ; DAXX : death-domain associated protein 6. This table contains the round 2 results.

Table 6. — **In which of the following clinical cases would you administer SSA as an adjuvant treatment?**

	YES	***NO***
CASE 1 - 27y old male after R0 resection (right hemicolectomy) of a pT3N2 well differentiated NET of the ileum (4 positive lymph nodes on a total of 15 resected, of which a mesenteric mass of 3.5cm; major lymphovascular invasion). Ki-67 3%. ECOG 0. No distant metastases on (postoperative) CT thorax/abdomen/pelvis. (n=16)	-	**100%** (16/16)
CASE 2 - 72y old male after R1 resection (whipple resection) of a well differentiated NET in the head of the pancreas pT3N0 (microscopic tumour invasion of posterior resection margin). Ki-67 12%. ECOG 1. No distant metastases on postoperative CT thorax/abdomen/pelvis. (n=16)	25% (4/16)	**75%** (12/16)
CASE 3 - 45y old female after synchronous R0 resection of a well differentiated NET in the tail of the pancreas and 4 liver metastases sized 2 to 4cm diameter. pT2N1M1. Ki-67 of 8% in the primary and up to 18% in the livermets. ECOG 0. No residual distant metastases on postoperative ^{68}Ga-DOTATATE-PET/CT. (n=16)	6.3% (1/16)	**93.7%** (15/16)
CASE 4 - 61y old male, diagnosed with siNET and 4 small sized synchronous liver metastases in segments 6 and 7 on ^{68}Ga-DOTATATE-PET. Patient is operated on with synchronous R0 resection of a pT3N1 well differentiated NET of the ileum (3 positive lymph nodes on a total of 12 resected; lymphovascular invasion present – primary Ki-67 1%) and parenchyma preserving liver resections of segments 6 and 7 showing actually 17 very small individual livermetastases on pathology– Ki-67 1-2%. ECOG 0. No residual distant metastases on postoperative ^{68}Ga-DOTATATE-PET/CT. (n=16)	12.5% (2/16)	**87.5%** (14/16)

SSA : somatostatin analogue ; y : year ; NET : neuroendocrine tumor ; ECOG : Eastern Cooperative Oncology Group performance status ; si: small intestine. This table contains the round 2 results. Bold characters are used when a consensus (≥ 75% of experts agreed or disagreed on a parameter) is obtained.

answers from round 1 were then voted upon in round 2, as presented in table 2, with a consensus reached on 80% (8/10) of these parameters. The same procedure was followed to judge on the prognostic impact of these NEN characteristics, as shown in table 3, reaching consensus on 66.7% (8/12) of parameters. Finally, experts were asked to rank a top 5 of prognostic NEN features according to importance in pancreatic primary (table 4) and in small intestinal primary (table 5). No prognostic parameter reached the consensus threshold with regards to individual order of importance. However, NEN staging and grading were consistently placed in the top 2 for both pNET (88.9% and 83.3% respectively) and siNET (77.7% and 77.8% respectively). Functional imaging was found to represent the third most important prognostic factor, reported in the top 3 by 83.2% of participants for pNET and by 72.2% for siNET. Apart from presence of the carcinoid heart disease, acknowledged prognostic parameters seem similar between pNET and siNET.

Table 7. — **Interference between non-radioactive and radioactive SSA**

1. Do you systematically interrupt SSA administration prior to planned ^{68}GA-DOTATATE-PET? (n=17)					
YES **82.3%** (14/17)		*NO* 11.8% (2/17)		*I don't know* 5.9% (1/17)	
2. Do you systematically interrupt SSA administration prior to planned PRRT cycle? (n=17)					
YES **94.1%** (16/17)		*NO* 5.9% (1/17)			
3. How long do you interrupt short-acting SSA prior to planned ^{68}GA-DOTATATE-PET? (n=16)					
8 hours 6.25% (1/16)	*24 hours* 56.25% (9/16)	*48 hours* 25% (4/16)	*1 week* 6.25% (1/16)	*I don't know* 6.25% (1/16)	
4. How long do you interrupt long-acting SSA prior to planned ^{68}GA-DOTATATE-PET? (n=17)					
4 weeks 58.8% (10/17)	*4-6 weeks* 23.5% (4/17)	*6 weeks* 5.9% (1/17)	*no interruption* 5.9% (1/17)	*I don't know* 5.9% (1/17)	
5. How long do you interrupt short-acting SSA prior to planned PRRT cycle? (n=16)					
8 hours 12.5% (2/16)	*24 hours* 37.5% (6/16)	*48 hours* 25% (4/16)	*8-48 hours* 6.25% (1/16)	*1-2 weeks* 6.25% (1/16)	*I don't know* 12.5% (2/16)
6. How long do you interrupt long-acting SSA prior to planned PRRT cycle? (n=17)					
4 weeks 52.9% (9/17)	*6 weeks* 11.8% (2/17)	*4-6 weeks* 17.7% (3/17)	*I don't know* 17.7% (3/17)		

SSA : somatostatin analogue ; PRRT : peptide receptor radionuclide therapy. This table contains the round 1 results. Bold characters are used when a consensus (≥ 75% of experts agreed or disagreed on a parameter) is obtained.

Topic 2 – Use of somatostatin analogues in adjuvant setting

In this topic the expert panel was challenged to describe in which clinical setting adjuvant treatment with SSA would be prescribed following NEN resection. When asked in an open question during round 1, 81.2% (13/16) would never consider SSA after complete surgical (R0) resection. 18.8% of experts would consider to do so in case of persistent hormonal symptoms (2/16) or lymph node positive disease (1/16), when SSTR-expression had been present preoperatively. In round 2, the experts were exposed to 4 (fictional) clinical cases including the same question (table 6). Overall, a consensus was observed not to administer SSA in all 4 cases. At live voting during round 3, a unanimous consensus (15/15) was reached to only administer postoperative SSA when visible residual disease was present on imaging, which is obviously not an adjuvant setting.

Topic 3 – Interference between non-radioactive and radioactive somatostatin analogues

Short- and long-acting SSAs target the same somatostatin receptors that are used by nuclear imaging and theragnostic techniques, like ^{68}Ga-DOTATATE positron emission tomography (PET) and PRRT. The concurrent use of non-radioactive and radioactive SSAs might interact and potentially disturb these diagnostic and therapeutic modalities. Panelists were asked if they were accustomed to systematically stopping SSA administration prior to SSTR-targeted imaging techniques and planned PRRT cycles. The optimal timing for interrupting SSA beforehand was then inquired upon. Already in round 1, there appeared to be a consensus to interrupt SSA for both imaging and therapeutic interventions (table 7). To test consistency in real practice the panelists were confronted with the following clinical case in round 2 : *"In a NET patient (non-functional) on long acting SSA 30mg every 4 weeks, a ^{68}Ga-DOTATATE PET appears to be planned 3 weeks after the last injection. Would you pick up the phone to reschedule the exam in this case or would you leave timing as it is?"*. Quite consistently, 77.8% (14/18) experts would reschedule the exam. During round 3, recent data were presented by the SC members challenging the dogma of the necessity to interrupt SSA prior to planned imaging, followed by group discussion (6,7). Afterwards, the same clinical case was re-voted upon. This time, 93.3% of attendees (13/14), including the 3 members of the SC, preferred to reschedule the exam. One attendee did not perform the live re-vote.

Topic 4 – Challenging small intestinal NET cases

In this topic, two (fictional) clinical cases of advanced siNET patients were presented to the panel in an open question during round 1, asking them to motivate their therapeutic strategy. In round 2, the experts were pushed to state their preferred sequential treatment of choice based on the results from round 1.

siNET case 1 : *"a 55y old female with a well differentiated, non-functional, jejunal NET (Ki-67 12%) with large mesenteric tumoral mass involving celiac trunk and superior mesenteric artery root and causing (secondary) venous congestion of the small bowel. The patient has diffuse abdominal pain after meals with secondary weight loss. R0 resection appears not to be feasible. No distant metastases on 3-phase CT thorax/abdomen/pelvis. ^{68}Ga-DOTATATE PET-CT is positive on the mesenteric mass."* The treatment options for this case included second opinion from a surgeon in a high-volume centre, everolimus, SSA, everolimus and SSA combination, cytotoxic chemotherapy and PRRT. Results are presented in figure 1. Many experts would recommend asking a surgical second opinion in an NEN

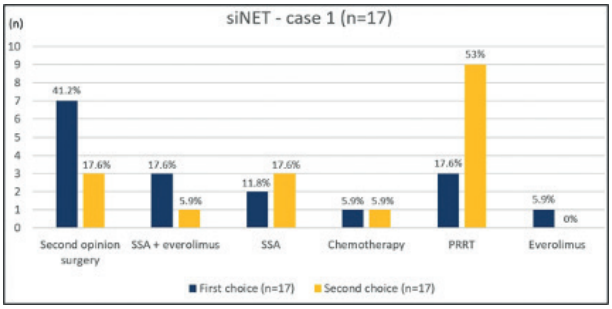

Figure 1 — Challenging siNET cases – case 1 siNET :small intestine neuroendocrine tumor, SSA : somatostatine analogue, PRRT : peptide receptor radionuclide therapy. This figure represents round 2 results.

expert centre. As most alternative therapeutic modalities will fail to induce tumor regression, the majority of the panel would go for PRRT treatment in the hope to achieve downsizing.

siNET case 2 : *"A 62y old male with a well differentiated, non-functional ileal NET (Ki-67 4%) with multiple lymph node, liver and bone metastases ; radiologically progressing on Octreotide LAR 30mg every 4 weeks after a period of 32 months of disease control under this therapy."* Therapeutic options available were : SSA dose increase and/or interval adjustment, switching SSA to everolimus, addition of everolimus to SSA, addition of interferon-α to SSA, addition of telotristat to SSA or rapid evaluation for PRRT. Experts were asked about the preferred sequential treatment of choice depending on whether or not a clinical carcinoid syndrome was present (figure 2). Based on the NETTER-1 trial, many experts would prefer doing a rapid evaluation for PRRT (8). SSA dose/interval modification and use of everolimus remain valued options in this case, probably reflecting the fact that PRRT is not reimbursed in Belgium and faces some accessibility issues.

Topic 5 – Therapeutic strategy in carcinoid syndrome

The carcinoid syndrome is one of the most common hormonal syndromes associated with NET, predominantly

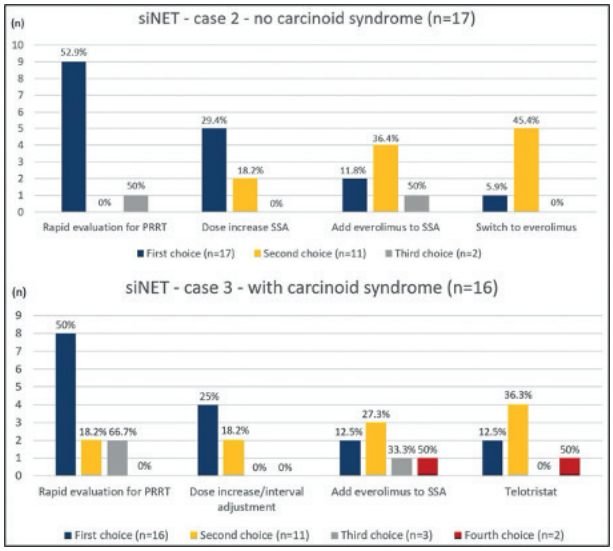

Figure 2 — Challenging siNET cases – case 2 siNET : small intestine neuroendocrine tumor, SSA : somatostatine analogue, PRRT : peptide receptor radionuclide therapy. This figure represents round 2 results.

siNETs. The SC created a (fictional) clinical case concerning an advanced siNET patient with carcinoid syndrome, initially well controlled on SSA, but later on developing refractory diarrhea. During round 1, experts were interrogated on their proposed clinical approach to the problem. Upfront diagnostic work-up for diarrhea, actively excluding alternative causes (infection, bile acid diarrhea, SSA induced steatorrhea, bowel ischemia, etc.) was considered by 41.2% (7/17) of experts. When diarrhea was indeed deemed attributable to refractory carcinoid syndrome, the preferred therapeutic approach appeared to differ substantially between experts when asked during round 2 (table 8).

Topic 6 – Chemotherapy use in advanced, well differentiated NET

Cytotoxic chemotherapy represents the oldest therapeutic strategy in NEN treatment and its efficacy and

Table 8 — **Therapeutic strategy in carcinoid syndrome**

"A 60y old female with a well differentiated ileal NET with Ki-67 = 6% (primary was resected through right hemicolectomy) and around 20 bilobar liver metastases. Patient initially presented with flushes and diarrhea 6 months ago. She received octreotide LAR 30mg i.m. every 4 weeks since then. After marked initial improvement in hormonal symptoms, she has been complaining of escalating bowel movement frequency (loose stools), progressively over the past 4 months, up to 12 times/day at present."					
	1st choice (n=17)	**2nd choice (n=15)**	**3rd choice (n=14)**	**4th choice (n=11)**	**5th choice (n=5)**
1. Telotristat	29.4% (5/17)	46.7% (7/15)	21.4% (3/14)	18.2% (2/11)	-
2. SSA dose increase	64.7% (11/17)	13.3% (2/15)	-	-	-
3. Locoregional therapy	5.6% (1/17)	13.3% (2/15)	14.3% (2/14)	27.2% (3/11)	20% (1/5)
4. PRRT	-	13.3% (2/15)	57.1% (8/14)	9.1% (1/11)	-
5. Everolimus	-	13.3% (2/15)	7.1% (1/14)	9.1% (1/11)	20% (1/5)
6. Sunitinib	-	-	-	9.1% (1/11)	-
7. Interferon-α	-	-	-	18.2% (2/11)	-
8. Debulking surgery	-	-	-	9.1% (1/11)	60% (3/5)

Y : year ; NET: neuroendocrine tumor ; SSA : somatostatin analogue ; PRRT : peptide receptor radionuclide therapy. This table contains the round 2 results.

Table 9. — **Parameters driving chemotherapy use in advanced, well differentiated NET**

	YES	***NO***
1. Primary tumor location (n=16)	62.5% (10/16)	37.5% (6/16)
- *pancreatic NET (n=9)*	***100%** (9/9)*	-
- *small intestinal NET (n=8)*	-	***100%** (8/8)*
- *pulmonary NET (n=9)*	*44.4% (4/9)*	*55.6% (5/9)*
- *oesophageal NET (n=9)*	*33.3% (3/9)*	*66.7% (6/9)*
- *gastric NET (n=9)*	*22.2% (2/9)*	***77.8%** (7/9)*
- *appendiceal NET (n=9)*	*22.2% (2/9)*	***77.8%** (7/9)*
2. Differentiation grade (n=16)	**93.8%** (15/16)	6.3% (1/16)
- *well differentiated (n=12)*	*25% (3/12)*	***75%** (9/12)*
- *poorly differentiated (n=14)*	***100%** (14/14)*	-
3. Proliferation index (n=16)	**93.8%** (15/16)	6.3% (1/16)
- *Ki-67 > 2% (n=10)*	*10% (1/10)*	***90%** (9/10)*
- *Ki-67 > 10% (n=11)*	*45.5% (5/11)*	*54.5% (6/11)*
- *Ki-67 > 20% (n=14)*	***85.7%** (12/14)*	*14.3% (2/14)*
- *Ki-67 > 40% (n=13)*	***100%** (13/13)*	-
- *Ki-67 > 60% (n=13)*	***100%** (13/13)*	-
4. Bulky/symptomatic disease (n=16)	**75%** (12/16)	25% (4/16)
5. Rapid progression (n=16)	**87.5%** (14/16)	12.5% (2/16)
6. ^{18}F-FDG-PET positivity (n=14)	**92.9%** (13/14)	7.1% (1/14)
7. Patient characteristics (n=16)	**87.5%** (14/16)	12.5% (2/16)
8. Neoadjuvant strategy (n=15)	46.7% (7/15)	53.3% (8/15)

NET : neuroendocrine tumor ; ^{18}F-FDG-PET : ^{18}F-fluorodeoxyglucose positron emission tomography. This table contains the round 2 results. Bold characters are used when a consensus (≥ 75% of experts agreed or disagreed on a parameter) is obtained.

Table 10 — **Preferred choice of chemotherapy regimen to treat advanced, well differentiated NET**

	Pancreatic NET	Small intestinal NET	Other NET
First line	n=16	n=15	n=15
capecitabine - temozolomide	43.7% (7/16)	27% (4/15)	26.7% (4/15)
oxaliplatin-5FU (folfox)	12.5% (2/16)	7% (1/15)	20% (3/15)
irinotecan-5FU (folfiri)	-	-	6.6% (1/15)
streptozocin (+/- 5FU)	18.8% (3/16)	-	-
I don't give chemotherapy	-	33% (5/15)	20% (3/15)
I don't know	25% (4/16)	33%(5/15)	26.7% (4/15)
Second line	n=15	n=14	n=14
capecitabine - temozolomide	6.7% (1/15)	-	7.1% (1/14)
oxaliplatin-5FU (folfox)	26.7% (4/15)	21.4% (3/14)	28.6% (4/14)
irinotecan-5FU (folfiri)	13.3% (2/15)	7.1% (1/14)	7.1% (1/14)
streptozocin (+/- 5FU)	20% (3/15)	7.1% (1/14)	7.1% (1/14)
platinum-etoposide	6.7% (1/15)	-	7.1% (1/14)
I don't give chemotherapy	-	28.7% (4/14)	7.1% (1/14)
I don't know	26.7% (4/15)	35.7% (5/14)	35.7% (5/14)

NET : neuroendocrine tumor ; 5-FU : 5-fluoro-uracil. This table contains the round 2 results.

limitations in this tumor type have been documented in clinical trials to some extent (9,10). This topic focused on the identification of those disease parameters that drove panelists to consider chemotherapy in the setting of advanced, well differentiated NET. Round 2 results are presented in table 9. 62.5% (10/16) of experts recognized primary tumor location as a determining factor in decision making. With regards to the preferred choice of chemotherapy regimen, a variety of answers were noted with capecitabine-temozolomide appearing to be the most popular regimen (table 10).

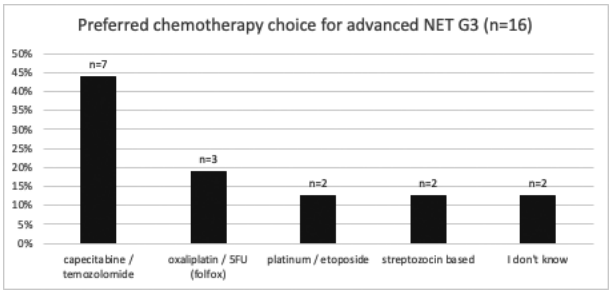

Figure 3 — What is your preferred cytotoxic chemotherapy choice in well-differentiated NET G3? NET G3 : neuroendocrine tumor grade 3, 5FU : 5-fluoro-uracil. This figure represents round 2 results.

Topic 7 – Grade 3 NET implications

Most recent WHO classification adjustments have introduced a newly defined subgroup of NET G3 to distinguish a subset of high grade, well differentiated NETs that show distinct differences from NECs concerning differentiation, proliferation index, molecular features, prognosis and response to chemotherapy (11). Although the new subclassification was introduced in pancreatic NENs only, it has already been extrapolated for all NEN primary locations by most pathologists' society guidelines (2). The optimal treatment strategy for this recent new subgroup of tumors remains to be investigated. Round 2 results showed 62.5% of the experts involved (10/16) feels the location of the primary tumor is of relevance when treating NET G3 patients. 86% of experts (12/14) feels a further subdivision of the NET G3 group, according to the Ki-67 proliferation index, will be relevant to refine optimal treatment options. Half of them suggests dividing Ki-67 below and above 50-55%, while the other half suggests 3 subdivisions between Ki-67 20 to 40%, 40 to 60% and above 60%. In lack of clear guidance in this setting, most experts would choose capecitabine-temozolomide as first choice chemotherapy option in NET G3 (figure 3).

Topic 8 – Imaging preferences in neuroendocrine neoplasms

Functional imaging techniques, mainly ^{18}F-FDG (fluorodeoxyglucose)- and ^{68}Ga-DOTATATE PET(CT) can play a pivotal role in diagnosis and management of NEN. The role of ^{18}F-FDG-PET is well established in poorly differentiated NEC, but less well documented in well differentiated NET. The round 2 expert opinion on the clinical value of ^{18}F-FDG-PET in this setting is summarized in table 11. The use of ^{68}Ga-DOTATATE PET(CT) appears to be mainly restricted to well differentiated NET and rarely advocated for NEC (table 12). On the contrary, the application of ^{18}F-FDG-PET(CT) is more widespread and is used for baseline prognostication as well as at the time of a change in clinical course, mainly in G2 & G3 NETs.

Table 11 — **Define the place of ^{18}F-FDG-PET in diagnosis and management of well differentiated NET**

	YES	***NO***
1. Baseline biological behaviour / prognostication	**93.8%** (15/16)	6.2% (1/16)
2. Bypass tumor heterogeneity (e.g. biopsy targeting)	**93.8%** (15/16)	6.2% (1/16)
3. Discrepancy in tumor behaviour over time and treatment lines	**93.8%** (15/16)	6.2% (1/16)
4. Therapy guidance in general (e.g. watchfull waiting, SSA, chemo, etc.)	68.8% (11/16)	31.3% (5/16)
5. Work-up before PRRT (SSTR-/FDG+ mismatch evaluation)	**81.3%** (13/16)	18.7% (3/16)
6. Response assessment		
- after PRRT	*53.3% (8/15)*	*46.7% (7/15)*
- after chemotherapy	***81.3%** (13/16)*	*18.7% (3/16)*
- after selective intrahepatic radiotherapy (SIRT)	***75%** (12/16)*	*25% (4/16)*
- after targeted agents (everolimus/sunitinib)	*50% (8/16)*	*50% (8/16)*

^{18}F-FDG-PET : ^{18}F-fluorodeoxyglucose positron emission tomography ; NET : neuroendocrine tumor ; SSA : somatostatin analogue ; chemo : cytotoxic chemotherapy ; PRRT : peptide receptor radionuclide therapy ; SSTR: somatostatin receptor. This table contains the round 2 results. Bold characters are used when a consensus (≥ 75% of experts agreed or disagreed on a parameter) is obtained.

Table 12 — **When would you advocate doing a PET(CT)-scan during NEN disease course?**

	AT DIAGNOSIS		**CHANGE IN CLINICAL COURSE**	
	^{68}GA-DOTA-PET	**^{18}F-FDG-PET**	**^{68}GA-DOTA-PET**	**^{18}F-FDG-PET**
1. NET GRADE 1	**93.7%** (15/16)	33.3% (5/15)	**100%** (16/16)	46.7% (7/15)
2. NET GRADE 2	**100%** (16/16)	40% (6/15)	**100%** (16/16)	**75%** (12/16)
3. NET GRADE 3	**87.5%** (14/16)	**100%** (16/16)	**87.5%** (14/16)	**100%** (16/16)
4. NEC	31.3% (5/16)	**93.8%** (15/16)	**18.8%** (3/16)	**81.3%** (13/16)

PET : positron emission tomography ; CT: computed tomography ; NEN : neuroendocrine neoplasm ; NET : neuroendocrine tumor ; NEC : neuroendocrine carcinoma ; ^{18}F-FDG : ^{18}F-fluorodeoxyglucose ; ^{68}GA-DOTA : ^{68}GA-DOTATATE. This table contains the round 2 results. Bold characters are used when a consensus (≥ 75% of experts agreed or disagreed on a parameter) is obtained.

Discussion

Optimal treatment stratification in NEN patients poses some major challenges. Many different disease and patient features need to be taken into account when choosing the 'right' treatment strategy for an individual patient. NENs are relatively rare and prove to be clinically and biologically heterogenous. The scientific pillars supporting our therapeutic armamentarium, on the other hand, show significant shortcomings. Clinical trial design and quality is nearly as heterogenous as the disease itself. For example, when analyzing both phase III trials comparing long-acting SSA to placebo, the progression free survival (PFS) for the placebo arm in the PROMID trial is 6 months, while in the CLARINET the PFS for the placebo arm reaches 18 months (12,13). It is clear that different patient populations have been included in these and other NEN trials, with marked differences in baseline inclusion criteria, trials are often underpowered, with unblinded design and different response assessment techniques used to measure efficacy. New treatments are generally compared to placebo or to a comparator of unknown efficacy, like the high dose SSA in the control arm of the NETTER-1 study (8). Qualitative head-to-head trials and treatment sequencing trials are currently lacking (though some are ongoing) and virtually no predictive biomarkers are available, except for SSTR imaging for PRRT (8,14).

The implementation of multidisciplinary team meetings (MDTM) is advocated as standard of care in modern oncology, especially when assessment and management require complex decision making. In the literature the impact of MDTMs is claimed to be associated with changes in staging/diagnosis, initial management plan, higher rates of treatment, shorter diagnosis to treatment interval, better survival and better adherence to clinical guidelines (15,16). However, despite being intuitively beneficial, these assumptions on MDTMs are based on retrospective and single center data with major selection bias. Few studies have looked at the fact whether the changes suggested in those MDTMs really impact outcome measures such as survival and the evidence is therefore regarded as very weak. Nonetheless, systematic implementation of MDTM in every Belgian center for oncological care might indeed have influenced more complete diagnostic work-up and better adherence to guidelines as suggested by the high level of concordance on relevant disease characteristics described in topic 1 and regarding non-radioactive and radioactive SSA interference in topic 3. In the latter topic, the vast majority of experts, 81.25% and 88.2% respectively, adhered to available guidelines recommending a cessation interval of at least 1 day for short-acting SSA and 3 to 4 weeks for long-acting analogues (17). With regards to planned PRRT cycles, respectively 81.25% and 82.3% of experts followed guidance to stop short-acting analogues at least 8 hours to 2 days before and long-acting analogues at least 4 to 6 weeks before (18-20). On the other hand, during the round 1 open question regarding diarrhea recurrence in a carcinoid syndrome patient (topic 5), an adequate upfront diagnostic work-up for diarrhea, actively excluding alternative causes (infection, bile acid diarrhea, SSA induced steatorrhea, bowel ischemia, etc.) was considered by only 41.2% (7/17) of experts, emphasizing the utility of continued expert discussions and multidisciplinarity.

When looking at therapeutic preferences in topic 4, 5 and 6, the lack of high-level scientific guidance appears to cause significant differences between experts and expert centers. It has been well documented that output of MDTMs depends on many factors, such as the composition of the participating faculty whose members might have had different training, different experience level and different working environment (21). But likely, in these specific 'grey area' cases, differences in treatment strategy are provoked by the low level scientific guidance available and the application of local 'institutional' guidelines, usually resulting from expert opinion of one (or a handful) MDTM participant(s).

In our opinion, the application of a modified Delphi approach has proven very useful as a vehicle to boost critical thinking and discussion among experts of different background and centers, as well as to describe current clinical practice and stimulate mutual learning. The anonymization of round 1 and 2 questionnaires and optimal question rephrasing help to really force participants to take personal statements on their daily practice. The more surprising or controversial answers or motivations given during round 1 could be used to fuel the round 3, face-to-face discussion when necessary. For some topics, the available scientific evidence, challenging some of the results, could be provided. For example, regarding the rather questionable prognostic impact of tumor functionality in topic 1 (22) and the relevance of primary tumor location in the administration of chemotherapy, quite surprisingly only deemed relevant to 62.5% of experts (topic 6) (9,23). Certain critical questions were raised and might offer insights for future discussions with health authorities e.g. on the extensive utility of PET-imaging techniques in the management of these patients (topic 8) and subsequent reimbursement. Whether all these additional evaluations implemented by MDTMs will eventually lead to better care, patient quality of life and survival, still remains an open question.

We deliberately avoided following a strict Delphi study model, striving towards consensus, which was not estimated useful nor possible in the absence of any evidence clearly promoting one treatment choice over the other. This strategic choice implies the main weakness of this approach and the resulting paper, largely reporting on what 'can' be done, rather than what 'should' be done. Due to the multidisciplinary composition of the expert panel and the controversial nature of the topics, several 'I don't know' answers were inevitable, weakening the strength of the results. Nonetheless, this type of Delphi-like multi-round expert meeting, describing

current practice and rationale, offers many educational opportunities and boosts critical evaluation of certain daily practice dogma's and guidelines.

Conclusion

We conducted a Delphi method-based, multidisciplinary expert discussion, digging into current clinical practice regarding controversial topics in NEN diagnosis and treatment. Overall, a high level of consensus was seen between experts, regarding the necessary diagnostic work-up for NEN and clinical guidelines appear to be followed consistently. In contrast, significant differences in treatment preferences and strategies are noticed between different experts and centers, when scientific evidence and guidance is lacking. The application of a Delphi-like multi-round expert discussion has proven very useful as a vehicle to boost critical thinking and discussion among experts of different background and centers, as well as to describe current clinical practice and stimulate mutual learning.

Acknowledgements

Novartis provided funding, but was not involved in the selection of panel experts, the choice of topics discussed, the interpretation of the data nor the compilation of the final manuscript.

XPE-Pharma & Science was contracted as independent vendor creating the electronical platform for the questionnaires and providing anonymized feedback of the answers to the steering committee.

Statement of ethics

The clinical cases used were fictional and created by the steering committee. No ethical approval or informed consent was applicable.

Disclosure statement

Pieter-Jan Cuyle, Consulting or advisory role : *Lilly, Novartis, Amgen, Roche, MSD, Pierre Fabre.*Travel expenses : *Novartis, Ipsen, Roche, Lilly* Karen Geboes Consulting or advisory role : *Ipsen, Novartis.* Research grant : *Ipsen, Advanced Accelerator Applications.* Travel expenses : *Ipsen, Novartis, Pfizer.* Saskia Carton Consulting or advisory role : *Lilly, Novartis.* Travel expenses : *Bayer, Ipsen.* Veerle Casneuf Consulting or advisory role : *Lilly, Merck.* Jochen Decaestecker No disclosures. Marc De Man Travel expenses : *Pfizer, Novartis.* Gauthier Demolin No disclosures. Christophe Deroose Consulting or Advisory Role : *Terumo, Advanced Accelerator Applications, Ipsen, Novartis, Sirtex, Bayer.* Caroline De Vleeschouwer No disclosures. Patrick Flamen No disclosures. Alain Hendlisz Research grant : *Ipsen, Bayer, Roche, Merck, Teva Pharma.* Anne Hoorens No disclosures. Jos Janssens No disclosures. Ioannis Karfis No disclosures. Willem Lybaert Consulting or advisory role : *Ipsen, Novartis.* Godelieve Machiels No disclosures. Els Monsaert No disclosures. Isabelle Sinapi No disclosures. Eric Van Cutsem Consulting or advisory role : *Array, Astrazeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daiichi, Halozyme, GSK, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier, Sirtex, Taiho.* Research grants : *Bayer, Boehringer Ingelheim, Celgene, Ipsen, Lilly, Roche, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier (paid to his institution).* Timon Vandamme Consulting or advisory role : *Ipsen, Novartis*, *Sirtex.* Ivan Borbath Travel expenses : *Ipsen, Pfizer, Bayer.* Consulting or advisory role : *Lilly, Servier, Eisai, Bayer, Ipsen, Novartis* Research grant : *Ipsen, Celgene.* Chris Verslype Consulting or advisory role : *Lilly, Novartis, Bayer, Ipsen.* Research grant : *Lilly, Novartis, Bayer, Ipsen.*

Funding sources

Financial support was provided by Novartis.

Author contributions

Conception and design *Pieter-Jan Cuyle, Ivan Borbath, Chris Verslype* Collection and assembly of data *Pieter-Jan Cuyle, Ivan Borbath, Chris Verslype* Data analysis and interpretation *Pieter-Jan Cuyle, Karen Geboes, Ivan Borbath, Chris Verslype* Provision of study materials *All authors* Manuscript writing *Pieter-Jan Cuyle, Karen Geboes, Christophe M. Deroose, Timon Vandamme, Ivan Borbath, Chris Verslype* Final approval of manuscript *All authors* Accountable for all aspects of manuscript *All authors.*

References

1. DASARI A, SHEN C, HALPERIN D, ZHAO B, ZHOU S, XU Y, *et al.* Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol.,* 2017, **3** : 1335-42.
2. RINDI G, KLIMSTRA DS, ABEDI-ARDEKANI B, ASA SL, BOSMAN FT, BRAMBILLA E, *et al.* A common classification framework for neuroendocrine neoplasms : an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod. Pathol.,* 2018, **31** : 1770-86.
3. CIVES M, STROSBERG JR. Gastroenteropancreatic Neuroendocrine Tumors. *CA Cancer J. Clin.,* 2018, **68** : 471-87.
4. LINSTONE H, TUROFF M. The Delphi method : techniques and applications. *Newark, New Jersey, USA : Institute of Technology, 2002*.
5. DIAMOND IR, GRANT RC, FELDMAN BM, PENCHARZ PB, LING SC, MOORE AM, *et al.* Defining consensus : a systematic review recommends methodologic criteria for reporting of Delphi studies. *J. Clin. Epidemiol.,* 2014, **67** : 401-9.
6. AALBERSBERG EA, DE WIT-VAN DER VEEN BJ, VERSLEIJEN MWJ, SAVEUR LJ, VALK GD, TESSELAAR MET, *et al.* Influence of lanreotide on uptake of (68)Ga-DOTATATE in patients with neuroendocrine tumours : a prospective intra-patient evaluation. *Eur. J. Nucl. Med. Mol. Imaging,* 2019, **46** : 696-703.
7. AYATI N, LEE ST, ZAKAVI R, PATHMARAJ K, AL-QATAWNA L, POON A, *et al.* Long-Acting Somatostatin Analog Therapy Differentially Alters (68) Ga-DOTATATE Uptake in Normal Tissues Compared with Primary Tumors and Metastatic Lesions. *J. Nucl. Med/,* 2018, **59** : 223-7.

8. STROSBERG J, EL-HADDAD G, WOLIN E, HENDIFAR A, YAO J, CHASEN B*, et al.* Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors. *N. Engl. J. Med.,* 2017, **376** : 125-35.
9. ANGELOUSI A, KALTSAS G, KOUMARIANOU A, WEICKERT MO, GROSSMAN A. Chemotherapy in NETs : When and how. *Rev. Endocr. Metab. Disord.,* 2017, **18** : 485-97.
10. KRUG S, GRESS TM, MICHL P, RINKE A. The Role of Cytotoxic Chemotherapy in Advanced Pancreatic Neuroendocrine Tumors. *Digestion,* 2017, **96** : 67-75.
11. CORIAT R, WALTER T, TERRIS B, COUVELARD A, RUSZNIEWSKI P. Gastroenteropancreatic Well-Differentiated Grade 3 Neuroendocrine Tumors : Review and Position Statement. *Oncologist,* 2016, **21** : 1191-9.
12. CAPLIN ME, PAVEL M, CWIKLA JB, PHAN AT, RADERER M, SEDLACKOVA E*, et al.* Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N. Engl. J. Med.,* 2014, **371** : 224-33.
13. RINKE A, MULLER HH, SCHADE-BRITTINGER C, KLOSE KJ, BARTH P, WIED M*, et al.* Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors : a report from the PROMID Study Group. *J. Clin. Oncol.,* 2009, **27** : 4656-63.
14. PAUWELS E, VAN BINNEBEEK S, VANDECAVEYE V, BAETE K, VANBILLOEN H, KOOLE M*, et al.* Inflammation-based index and (68)Ga-DOTATOC PET-derived uptake and volumetric parameters predict outcome in neuroendocrine tumor patients treated with (90)Y-DOTATOC. *J. Nucl. Med.,* 2019.
15. BASTA YL, BOLLE S, FOCKENS P, TYTGAT K. The Value of Multidisciplinary Team Meetings for Patients with Gastrointestinal Malignancies : A Systematic Review. *Ann. Surg. Oncol.,* 2017, **24** : 2669-78.
16. PILLAY B, WOOTTEN AC, CROWE H, CORCORAN N, TRAN B, BOWDEN P*, et al.* The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings : A systematic review of the literature. *Cancer Treat. Rev.,* 2016, **42** : 56-72.
17. BOZKURT MF, VIRGOLINI I, BALOGOVA S, BEHESHTI M, RUBELLO D, DECRISTOFORO C*, et al.* Guideline for PET/CT imaging of neuroendocrine neoplasms with (68)Ga-DOTA-conjugated somatostatin receptor targeting peptides and (18)F-DOPA. *Eur. J. Nucl. Med. Mol. Imaging*, 2017, **44** : 1588-601.
18. BODEI L, MUELLER-BRAND J, BAUM RP, PAVEL ME, HORSCH D, O'DORISIO MS*, et al.* The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur. J. Nucl. Med. Mol. Imaging,* 2013, **40** : 800-16.
19. HICKS RJ, KWEKKEBOOM DJ, KRENNING E, BODEI L, GROZINSKY-GLASBERG S, ARNOLD R*, et al.* ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia : Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. *Neuroendocrinology,* 2017, **105** : 295-309.
20. POEPPEL TD, BOY C, BOCKISCH A, KOTZERKE J, BUCHMANN I, EZZIDDIN S*, et al.* [Peptide receptor radionuclide therapy for patients with somatostatin receptor expressing tumours. German Guideline (S1)]. *Nuklearmedizin,* 2015, **54** : 1-11, quiz N2.
21. EL SAGHIR NS, KEATING NL, CARLSON RW, KHOURY KE, FALLOWFIELD L. Tumor boards : optimizing the structure and improving efficiency of multidisciplinary management of patients with cancer worldwide. *Am. Soc. Clin. Oncol. Educ. Book,* 2014 : e461-6.
22. ZANDEE WT, KAMP K, VAN ADRICHEM RC, FEELDERS RA, DE HERDER WW. Effect of hormone secretory syndromes on neuroendocrine tumor prognosis. *Endocr. Relat. Cancer,* 2017, **24** : R261-R74.
23. LAMARCA A, ELLIOTT E, BARRIUSO J, BACKEN A, MCNAMARA MG, HUBNER R*, et al.* Chemotherapy for advanced non-pancreatic well-differentiated neuroendocrine tumours of the gastrointestinal tract, a systematic review and meta-analysis : A lost cause? *Cancer Treat. Rev.,* 2016, **44** : 26-41.